18th Annual Meeting, American College of Chest Physicians
Congress Hotel, Chicago, Illinois, June 5 - 8, 1952

VOLUME XXI NUMBER 4

DISEASES

of the

CHEST

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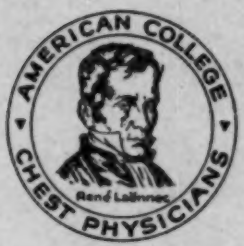

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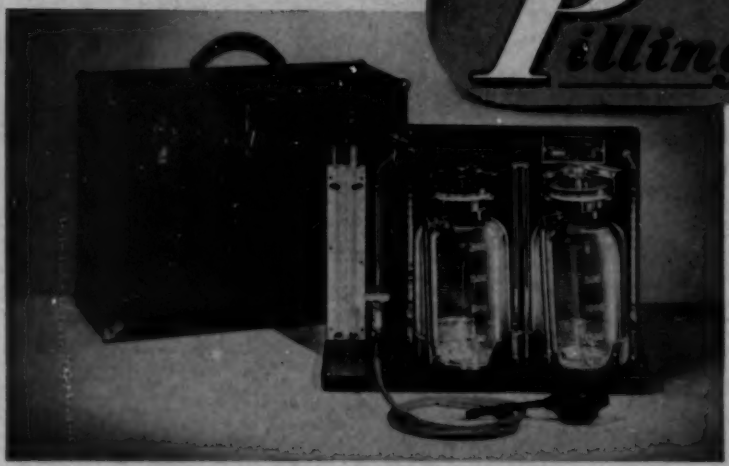

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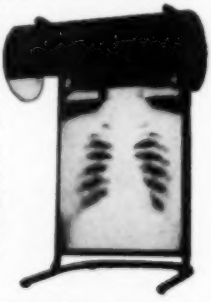

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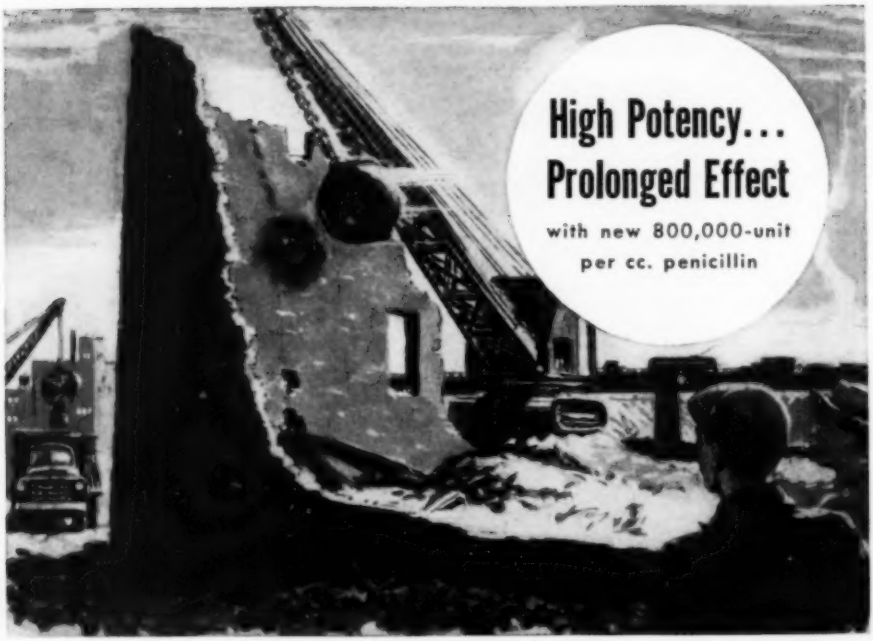

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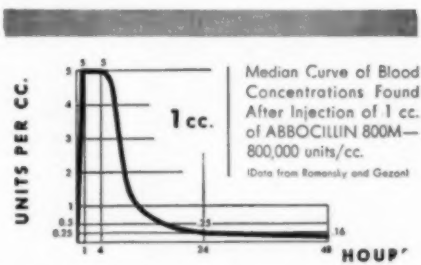

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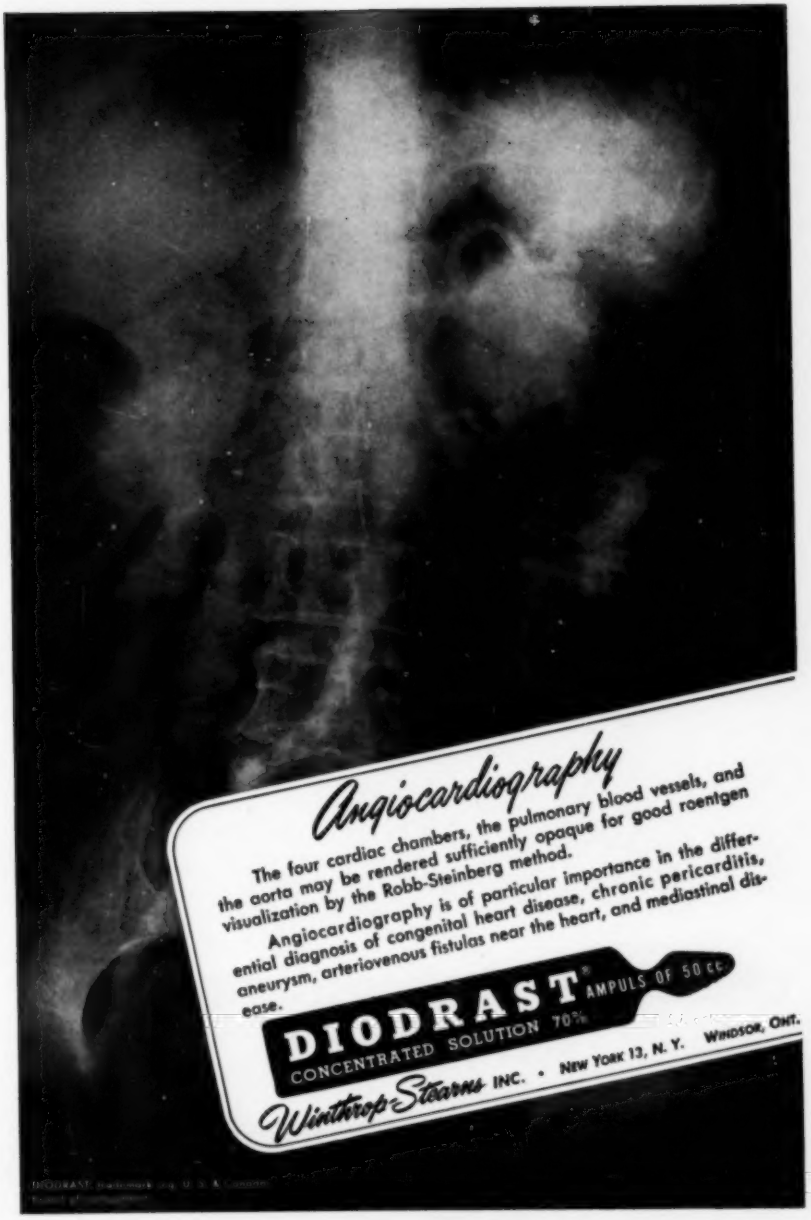
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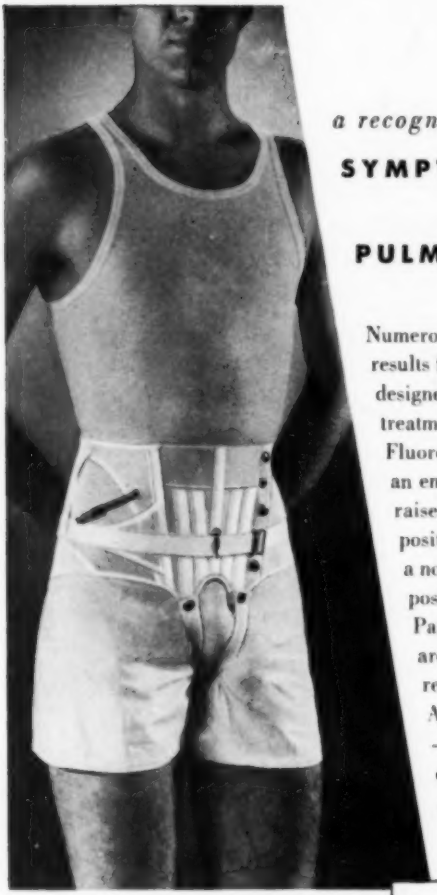

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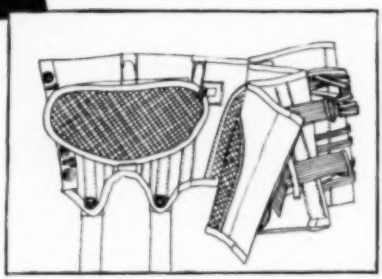

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1. J.A.M.A. 147:730-737 (Oct. 20) 1951. Literature and detailed dosage information on request.

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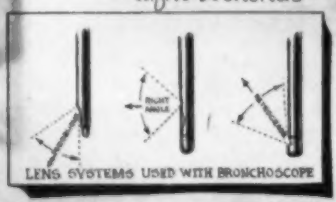

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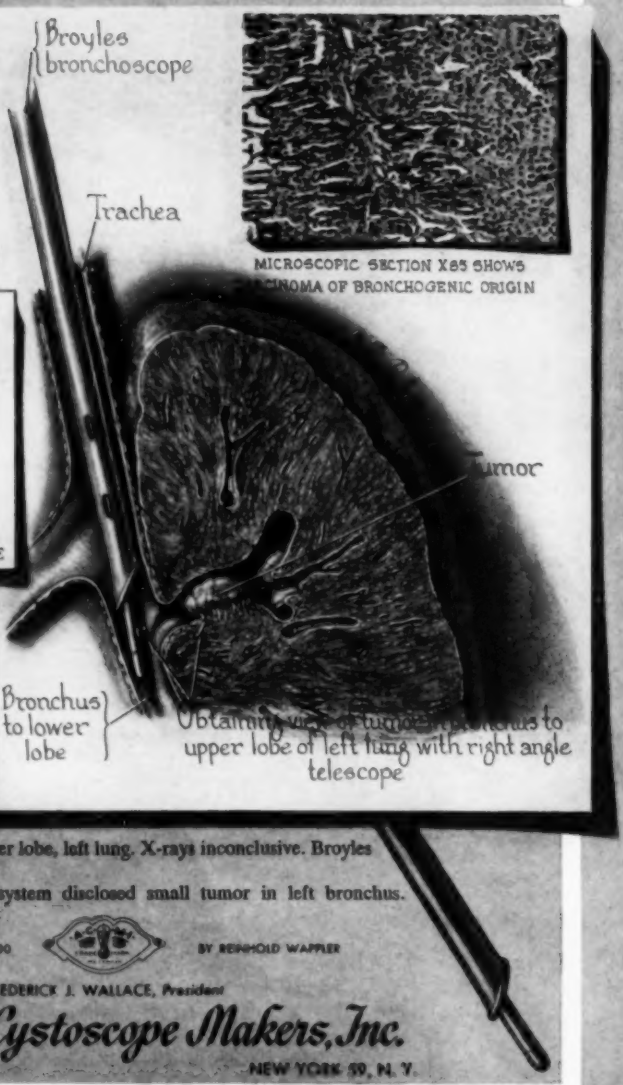
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DISEASES *of the* CHEST

VOLUME XXI APRIL 1952 NUMBER 4

On the Lasting Protective Effect of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis Infection of Mice*

E. GRUNBERG, B. LEIWANT, L-L. D'ASCENSIO and R. J. SCHNITZER†
Nutley, New Jersey

In an earlier paper,[1] the properties of isonicotinic acid hydrazide (Rimifon)* and its isopropyl derivative (Marsilid)* were described in relation to their protective effect in the experimental infection of mice with M. tuberculosis H37Rv. These compounds seemed to possess two characteristics unknown in any of the antituberculous agents previously described: 1) they appeared quantitatively considerably more effective than streptomycin, tibione and related substances and particularly para-aminosalicylic acid and niacinamide; and 2) in mice treated for the commonly used period of 21 days not only were tuberculous lesions absent but viable tubercle bacilli were either absent or so few in number at certain dosage ranges that they could no longer be demonstrated by cultures from the lungs. The unusual observation of negative cultures, which according to the literature and our own experience cannot be expected after the use of merely tuberculostatic agents, prompted the present study on the fate of mice infected with M. tuberculosis, treated for a period of 21 days and then held for an additional observation period of 21 days without any medication. In this investigation drugs of known antitubercular activity both experimentally and clinically such as streptomycin, para-aminosalicylic acid, tibione as well as the thiosemicarbazone of nicotinaldehyde and isonicotinaldehyde were

*These compounds were synthesized by Dr. H. H. Fox in the Roche Chemical Research Laboratories.

†Chemotherapy Laboratories, Hoffmann-La Roche Inc., Nutley, N. J.

Submitted for publication, January 19, 1952.

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included. The activity of the last two compounds has been described in a recent paper by Grunberg et al.[2] which also confirmed the data published by Levaditi and his co-workers[3] on the thiosemicarbazone of nicotinaldehyde.

Material and Methods

The H37Rv strain of M. tuberculosis obtained through the courtesy of Mr. W. Steenken, Jr., of Trudeau Sanatorium on December 20, 1947, was used in all experiments.

The technique of evaluating the compounds in vivo consisted of the same method described previously[2] with one modification. This involved an extension of the observation time. In these tests the animals were observed following the 21 day treatment period for an additional 21 days during which time they received a normal non-medicated diet consisting of Borden's Chunx. Fatalities during this period were noted and at the end of the 42 days all animals surviving were sacrificed and examined for gross lesions and whenever possible cultures were taken on egg-potato medium.[4]

Experimental Results

The results of the investigations are compiled in Tables I-IV. The data in these tables represent not only the gross findings in the lungs of successfully and unsuccessfully treated animals as well as of the controls but also the mortality rate and extent of lung involvement. We would like to point out that the term protection as used in Tables I and III in the expression "mice protected" refers to the complete absence of gross lesions in the lungs, a fact which was corroborated by the study of tissue sections of these organs as far as they have been carried out to the present moment. It also means that cultures taken from these lungs did not show any growth after the extended observation time. Moreover, the figures in the tables refer only to the mice which were examined at time of death if it occurred at least 10 to 14 days after infection or to those sacrificed at the end of the 42 days observation period.

The data presented in Table I seem to indicate that para-aminosalicylic acid, tibione and the thiosemicarbazone of nicotinaldehyde and isonicotinaldehyde did not produce a lasting protection in the intravenous type of infection although very high doses were employed. Only the high doses showing an absence of activity have been listed in the table; they belong to considerably larger series of experiments in which smaller doses were also employed and obviously found to be without effect. The failure of streptomycin might, however, be due to the comparatively small dose

employed although other investigators e.g. Levaditi et al.,[5] Baker et al.[6] and Youmans et al.[7] have shown that even considerably higher doses failed to kill the bacilli or prevent the death of mice infected with either human or bovine strains of M. tuberculosis. The two hydrazine derivatives, on the other hand, exhibited a quite marked activity even in a dosage range much lower than that employed for the other orally administered anti-tubercular agents. Doses of 50.0 mg./K. in case of Rimifon and 25.0 mg./K. in case of Marsilid protected approximately 50 per cent of the animals and rendered them completely free of lesions. Lower doses, although they did not produce protection in a significant number of animals, seemed to exert, nevertheless, a marked effect on the life span and the severity of pulmonary lesions of the infected mice. This is shown in Table II. In Table II only the data of the markedly active compounds, Rimifon and Marsilid, are

TABLE I

Comparison of Activity of Known Anti-tubercular Agents with Rimifon and Marsilid in the "Hold-Over" Intravenous Infection of Mice with M. Tuberculosis H37Rv

Treatment: Medicated diet for 21 days. Normal diet for 21 days.

COMPOUND	Daily Dose mg./kg.	Number of Mice	MICE PROTECTED Number	MICE PROTECTED Percentage
Streptomycin	50.0*	7	0	0.0
Para-aminosalicylic acid	2500.0	26	0	0.0
Tibione	2500.0	8	0	0.0
Nicotinaldehyde thiosemicarbazone	500.0	8	0	0.0
Isonicotinaldehyde thiosemicarbazone	500.0	17	0	0.0
Rimifon	250.0	72	53	73.7
	50.0	39	19	48.7
	25.0	44	11	25.0
	12.5	19	2	10.5
	3.12-6.25	15	1	6.6
Marsilid	500.0	17	12	70.6
	250.0	35	23	65.7
	100.0	29	22	75.9
	50.0	26	13	50.0
	25.0	20	10	50.0
	6.25-12.5	20	0	0.0
Controls	—	113	0	0.0

*Single daily treatment subcutaneously for 21 days.
No treatment for 21 days.

given. The grading of the pulmonary involvement is similar to that suggested by Youmans[8] and the final figure given represents the average degree of the extent of tuberculous lesions.

The data concerning mortality rate clearly show that at the end of the observation period of 42 days, the majority (81.7 per cent) of the untreated controls had succumbed. The death rate in the dosage range 12.5-250.0 mg./K. was negligible in case of Rimifon. With Marsilid a low mortality was observed with even the lowest doses (6.25 mg./K.).

The observation on the pulmonary involvement is in good agreement with both the protection rate and survival time. Both compounds appear still markedly active in the dosage range of 25.0 mg./K.

In corresponding experiments using the intranasal infection with M. tuberculosis H37Rv, the overall picture of the protective effects of the two new compounds was similar to those observed in the intravenous infection. Table III is meant to demonstrate the protective effect of different anti-tubercular agents in comparison with Rimifon and Marsilid. The results are again based on the absence of pulmonary lesions at the end of the 42 day observation period or 21 days after the discontinuation of therapy.

In evaluating these results it might be remembered that the course of the intranasal infection is as a rule milder[1] although

TABLE II

Mortality and Degree of Pulmonary Involvement in Mice Infected Intravenously with M. Tuberculosis H37Rv and Treated with Rimifon or Marsilid for 21 Days

Observation Period: 42 Days

COMPOUND	Dose mg./kg./day	Number of Mice	Per cent Mortality	Average Pulmonary Involvement*
Rimifon	250.0	72	2.8	0.55
	50.0	39	8.0	0.95
	25.0	44	0.0	1.6
	12.5	19	0.0	2.5
	3.12-6.25	15	40.0	3.4
Marsilid	500.0	17	0.0	0.6
	250.0	35	0.0	0.63
	100.0	29	0.0	0.48
	50.0	26	0.0	1.23
	25.0	20	0.0	1.4
	6.25-12.5	20	5.0	3.2
Controls	—	113	81.7	3.94

*s/n: s=sum of extent of pulmonary lesions (0, 1+, 2+, 3+, 4+).
n=number of animals.

more resistant to treatment with certain drugs.[3] Corresponding to this experience para-aminosalicylic acid was completely inactive. This is not surprising since this compound is not able to suppress the intranasal infection even during the time the drug is administered. Tibione, nicotinaldehyde thiosemicarbazone and isonicotinaldehyde thiosemicarbazone, which as described before[3] are able to suppress the lesions for the duration of treatment, were also ineffective after discontinuance of treatment. Rimifon and Marsilid, on the other hand, protected the majority of animals with a dose as low as 12.5 mg./K.

These observations are supplemented by the data in Table IV, in which again the inactive compounds have been omitted. It also seemed unnecessary to list the mortality rate which even in case of the untreated controls was not higher than 8 per cent. In agreement with our earlier observations[1] on the higher sensitivity of the intranasal infection to the group of hydrazine derivatives of isonicotinic acid, the inhibiting influence of the two new compounds on the spreading of the tuberculous lesions was more marked than was the case in the intravenous infection. Definite

TABLE III

Comparison of Activity of Known Anti-tubercular Agents with Rimifon and Marsilid in the "Hold-Over" Intranasal Infection of Mice with M. Tuberculosis H37Rv

Treatment: Medicated diet for 21 days. Normal diet for 21 days.

COMPOUND	Daily Dose mg./kg.	Number of Mice	MICE PROTECTED Number	MICE PROTECTED Percentage
Tibione	2500.0	6	0	0.0
Nicotinaldehyde thiosemicarbazone	500.0	9	1	11.1
Isonicotinaldehyde thiosemicarbazone	500.0	19	1	5.3
Rimifon	250.0	62	56	90.3
	50.0	51	47	92.2
	25.0	51	42	82.4
	12.5	17	14	82.3
	6.25	10	0	0.0
Marsilid	500.0	25	23	92.0
	250.0	37	35	94.6
	100.0	28	26	92.9
	50.0	27	22	81.5
	25.0	20	12	60.0
	12.5	18	12	66.6
	6.25	10	0	0.0
Controls	—	74	4	5.7

differences as compared to the controls were seen at a dose of 12.5 mg./K. with both Rimifon and Marsilid.

It might be mentioned that under the conditions of the intranasal infection the parenteral treatment with Rimifon and Marsilid given only once daily by the subcutaneous route was equally as effective as oral administration by diet which results in a more continuous medication. By the subcutaneous treatment schedule given for 21 days at which time the drug was discontinued and the animals observed for an additional 21 days, a dose of 50.0 mg./K. Rimifon or Marsilid kept 90 to 100 per cent of the animals alive and free of lesions. The same dose of streptomycin was entirely inactive.

Discussion

The results with Rimifon and Marsilid presented in the experimental section of this paper supplement the data given in our previous report.[1] The earlier findings as to the marked reduction or absence of viable tubercle bacilli in successfully treated animals are corroborated by the present observations that a high percentage of mice treated with doses that are known to render them culturally free of bacilli also do not develop tuberculous lesions in the lungs even after discontinuance of treatment and observation for a period sufficient in which lesions may develop. This seems to indicate that the majority of the causative organ-

TABLE IV

Degree of Pulmonary Involvement in Mice Infected Intranasally with M. Tuberculosis H37Rv and Treated with Rimifon or Marsilid for 21 Days

Observation period: 42 days

COMPOUND	Dose, mg./kg./day	Number of Mice	Average Pulmonary Involvement*
Rimifon	250.0	62	0.13
	50.0	51	0.17
	25.0	51	0.41
	12.5	17	0.24
	6.25	10	3.5
Marsilid	500.0	25	0.12
	250.0	37	0.02
	100.0	28	0.31
	50.0	27	0.33
	25.0	20	1.15
	12.5	18	1.08
	6.25	10	3.77
Controls	—	74	3.26

*s/n: s=sum of extent of pulmonary lesions (0, 1+, 2+, 3+, 4+). n=number of animals.

isms present at the time of infection were sufficiently damaged so as to prevent the development of lesions after discontinuance of medication. Whether or not the tubercle bacilli present in the mice are actually killed is difficult to decide and any statement as to this point will have to await further experiments with more sensitive methods, even though Steenken and Wolinsky's experiments[9] also suggest tuberculocidal properties for the new agents.

As in earlier experiments, the milder intranasal infection responded more readily to the two new compounds. This is evident from the approximate 50 per cent protective doses which in case of the intranasal infection were roughly one-fourth to one-half of that obtained with the intravenous infection. The possible explanation for this observation has been discussed in our earlier paper.[1]

The extent of our present observations does not seem to allow a definite conclusion as to whether or not a significant difference in activity exists between Rimifon and Marsilid. There seems to be no doubt, however, that the two new agents exert a type of activity not observed so far with any of the known anti-tubercular agents.

SUMMARY

1) A group of experiments is presented in which mice infected with M. tuberculosis H37Rv by the intravenous or intranasal route received treatment with different anti-tubercular agents for a 21 day period. The success or failure of this treatment was evaluated after an additional 21 day period without any drug administration.

2) Under these experimental conditions, known anti-tubercular agents such as streptomycin, para-aminosalicylic acid, tibione, nicotinaldehyde thiosemicarbazone and isonicotinaldehyde thiosemicarbazone given in doses high enough to protect the mice for the duration of treatment did not prevent an extensive lung involvement after the discontinuance of therapy.

3) Two new anti-tubercular compounds, namely, isonicotinic acid hydrazide, Rimifon, and its isopropyl derivative, Marsilid, on the other hand, prevented in comparatively low dosage ranges the development of the tuberculous lesions in the lungs of a substantial number of the animals observed for the extended period of time. In addition, a marked influence on the mortality rate was observed in case of the intravenous infection.

4) The indications are, therefore, that the results obtained with Rimifon and Marsilid are due to a direct effect on the viability of the causative organisms. However, no claim can be made at the present time that a permanent sterilization of the infected host has been achieved.

RESUMEN

1) Se presenta un grupo de experimentos en el cual ratones infectados con Micobacterium tuberculosis H37Rv por la vía intravenosa o intranasal recibieron tratamiento con diferentes agentes antituberculosos por un periodo de 21 días. El éxito o el fracaso de este tratamiento fué evaluado en un periodo adicional de 21 días sin administrarse ninguna droga.

2) Bajo estas condiciones experimentales, los agentes antituberculosos conocidos como la estreptomicina, ácido para-aminosalicílico, amitiozona, nicotinaldehido tiosemicarbazona e isonicotinaldehido tiosemicarbazona dados en dosis suficientemente altas para proteger a los ratones durante la duración del tratamiento no previno una extensa invasión del pulmón después de la suspensión de la terapia.

3) Dos nuevos compuestos antituberculosos, que son el ácido isonicotínico hidrazida, Rimifón, y su derivado isopropilo, Marsilida, por otra parte previnieron en dosis comparativamente bajas el desarrollo de las lesiones tuberculosas del pulmón, en un número considerable de animales observados en un largo periodo de tiempo. Además fué observada una marcada influencia en el promedio de mortalidad en casos de infección intravenosa.

4) Las indicaciones son por lo tanto que los resultados obtenidos con Rimifón y Marsalida son debidos al efecto directo en la vitalidad de los organismos causantes. Sin embargo no se puede decir todavía que la esterilización permanente del huesped infectado se ha logrado.

RESUME

1) Les auteurs rapportent le résultat du traitement par différents agents antituberculeux pendant 21 jours d'une série de souris infectées expérimentalement par la souche de bacilles tuberculeux H37Rv, soit par voie intra-veineuse, soit par voie intra-nasale. Les résultats de ce traitement furent appréciés après una période supplémentaire de 21 jours pendant lesquels aucun traitement ne fut fait.

2) Dans ces conditions expérimentales, les agents antituberculeux connus, tels que streptomycine, P.A.S., amithiazone, nicotinaldehyde, thiosemicarbazone et isonicotinaldehyde thiosemicarbazone furent donnés à des doses suffisamment élevées pour protéger les souris pendant toute la durée du traitement. Toutefois ces doses ne permirent pas d'éviter une évolution tuberculeuse extensive à partir du moment où fut cessé le traitement.

3) Deux nouveaux composés antituberculeux, l'acide hydrazide isonicotinique ("Rimifon") et son dérivé isopropyle ("Marsilid")

avec des doses relativement faibles ont évité le développement des lésions tuberculeuses des poumons chez un nombre important des animaux, surtout pendant la période de l'évolution des lésions. De plus, une influence notable sur le pourcentage de mortalité s'observa dans les cas où l'infection expérimentale avait été provoquée par voie intra-veineuse.

4) Les résultats obtenus par le "Rimifon" et le "Marsilid" sont dus à l'effet direct que l'on obtient grâce à ce produit sur la vitalité des microbes responsables. Cependant, il est impossible d'affirmer pour le moment qu'on a obtenu ainsi une stérilisation permanente des microbes introduits dans l'organisme.

REFERENCES

1 Grunberg, E. and Schnitzer, R. J.: "Studies on the Activity of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice," *Quart. Bull.*, Sea View Hosp., 13:3, 1952.
2 Grunberg, E. and Leiwant, B.: "Anti-tubercular Activity in Vivo of Nicotinaldehyde Thiosemicarbazone and Its Isomers," *Proc. Soc. Exp. Biol. and Med.*, 77:47, 1951.
3 Levaditi, C., Girard, A., Vaisman, A. and Ray, A.: "Etude Experimentale de l'Activité Anti-tuberculeuse de la *B* Pyridine Aldehyde Thiosemicarbazone," *C. r. Acad. Sci.*, 231:1174, 1950.
4 Sasano, K. T. and Medlar, E. M.: "Egg-Yolk-Potato-Medium," *Am. Rev. Tuberc.*, 48:297, 1943.
5 Levaditi, C., Vaisman, A. and Lévy, R.: "Traitement des Souris Tuberculisées par de Fortes Doses de Streptomycine," *C. r. Acad. Sci.*, 226: 1759, 1948.
6 Baker, M. J., Schlosser, M. E. and White, H. J.: "A Method for Evaluating Anti-tubercular Activity in Mice," *Ann. N. Y. Acad. Sci.*, 52:678, 1949.
7 Youmans, G. P., Williston, E. H. and Osborne, R. R.: "Occurrence of Streptomycin Resistant Tubercle Bacilli in Mice Treated with Streptomycin," *Proc. Soc. Exp. Biol. and Med.*, 70:36, 1949.
8 Youmans, G. P.: "The Use of the Mouse for the Testing of Chemotherapeutic Agents Against Mycobacterium Tuberculosis," *Ann. N. Y. Acad. Sci.*, 52:662, 1949 .
9 Steenken, W., Jr. and Wolinsky, E.: "Anti-tuberculous Properties of Hydrazines of Isonicotinic Acid," *Am. Rev. Tuberc.*, In press.

Tolerance of Macacus Rhesus for Isonicotinylhydrazines*

A Preliminary Report

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Introduction

The finding that isonicotinylhydrazines are effective in the treatment of experimental tuberculosis in mice[1] rabbits and guinea pigs[2] and the additional information that the protective effect was of lasting duration[3] led to the performance of toxicity studies in rats and dogs. One or the other of these species showed some evidence of damage to the liver, kidneys or hematopoetic organs of animals that were given as little as 1 mg./K. of the parent compound, isonicotinylhydrazine, as little as 3.5 mg./K. of alkyl derivative, 1-isonicotinyl-2-isopropylhydrazine, and as little as 5 mg./K. glucosyl, 1-isonicotinyl-2-glucosylhydrazine.[4] Before these compounds were administered to human subjects it was deemed prudent to make toxicity studies in Macacus rhesus monkeys which form the basis of this preliminary report.

Methods

The monkeys were housed at the Yale Colony. Food and water were furnished ad libitum. The general condition of the animals was observed daily. The body weights were determined at intervals of approximately one month. The hemoglobin concentration of the blood was measured with the aid of a Spencer hemoglobinometer at similar intervals. The compounds under study were administered either orally as sugar coated tablets or intraperitoneally in dilute solution.

The three compounds tested were:

1-isonicotinyl-2-glucosylhydrazine (Ro2-4179).†
isonicotinylhydrazine (Ro2-3973) RIMIFON.
1-isonicotinyl-2-isopropylhydrazine (Ro2-4572) MARSILID.

The choice of dosage was based upon antitubercular activity levels demonstrated in mice[1-3] and toxicity tests in rats and dogs.[4]

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*From the Department of Clinical Research, Hoffmann-La Roche, Inc., Nutley, New Jersey, and the Aeromedical Research Unit, Yale University School of Medicine, New Haven, Connecticut.

†These compounds were synthesized in the Scientific Laboratories of Hoffmann-La Roche, Inc., Nutley, New Jersey, by H. H. Fox.

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Only one monkey has been autopsied, the second animal being saved for a more prolonged period of study and the third was spared so that if pathological changes were found their reversability might be determined.

Results

The intraperitoneal injection of 10 mg./K. of isonicotinylglucosylhydrazine for 28 days had no adverse effect upon general behavior, body weight or hemoglobin concentration (Table I). When the dose was raised to 25 mg./K. for 18 days or 33 mg./K. for 47 days no adverse effects were noted.

The oral administration of 5 mg./K. of isonicotinylhydrazine for 44 days did not cause any change in general behavior but was noted to have produced a slight weight loss in one monkey of the three and a slight fall in the hemoglobin level in another animal (2.0 gm.).

When the animals were shifted to isonicotinylisopropylhydrazine, first at 7 mg./K. for 48 days, next at 14 mg./K. for 10 days and then at 18 mg./K. for 12 weeks (equivalent to 10, 20 and 25 mg./K. of the dihydrochloride of isonicotinylisopropylhydrazine as re-

TABLE I

Effect of Isonicotinylhydrazines Upon Body Weight and Hemoglobin Level of Three Macacus Rhesus Monkeys

Date	Drug	Route	Dose mg./K.	WEIGHT K.			HEMOGLOBIN gm./100 cc.		
				No.1-2	No.2-2	No.2-3	No.1-2	No.2-2	No.2-3
3/20	None	—	—	2.3	2.7	2.4	13.0	13.4	12.4
4/16	Isonicotinylglucosylhydrazine	i.p.	10	2.3	2.8	2.4	12.5	13.2	11.8
5/12	None	—	—	2.4	3.4	2.6	13.5	14.1	12.2
6/13	Isonicotinylglucosylhydrazine	i.p.	25	2.5	3.5	2.8	13.5	13.3	12.1
7/31	Isonicotinylhydrazine	p.o.	5	2.6	3.0	2.9	11.5	12.2	12.2
10/3	Isonicotinylglucosylhydrazine	i.p.	33	2.9	3.4	3.0	13.0	13.5	13.0
10/20	Isonicotinylisopropylhydrazine	i.p.	7	3.0	3.6	3.0	13.0	13.2	13.5
11/14	Isonicotinylisopropylhydrazine	i.p.	14	—	—	—	—	—	—
12/14	Isonicotinylisopropylhydrazine	i.p.	18	3.3	3.8	3.1	13.2	12.5	13.2
1/11	Isonicotinylisopropylhydrazine	i.p.	18	—	3.7	—	—	12.2	—

ported in the studies on rats and dogs) there were no external evidences of intolerance. The monkeys gained weight and the changes in hemoglobin level were within the range of experimental error.

Autopsy on Monkey (Tattoo 574, January 11, 1952)*

Gross Notes

The animal is in a good state of nourishment and weighs 3665 grams. The only gross changes of note are in the peritoneum where there are a few thin fibrous adhesions and a small quantity of chocolate colored fluid. These changes are the probable result of repeated intraperitoneal injections received by this animal. The weights of the organs are as follows:

Heart — 14.5 gm.
Lungs — 22 gm.
Liver — 105 gm.
Spleen — 5.5 gm.
Adrenals — 1 gm. (combined weight)
Kidneys — Left, 7.2 gm.; Right, 7.2 gm.
Thymus — 7 gm.

Microscopic Notes

Heart: There are no changes in the epicardium. The myocardial fibers are everywhere clearly striated and have centrally placed nuclei. There is no interstitial exudate. The endocardium is thin and delicate.

Lungs: Two large pulmonary sections are examined. These appear to be entirely normal in every respect except for small accumulations of large mononuclear cells containing black or olive colored finely granular pigment. These fill scattered small groups of alveoli. For the most part the latter appear empty. There are lymphoid follicles of moderate size in association with the large bronchi. The follicles have large germinal centers. The epithelium of the bronchi is intact and there are no vascular changes.

Spleen: The capsule and trabeculae have the usual wavily fibrillar structure. The malpighian corpuscles are large and have prominent germinal centers. The sinusoids are not congested and there are no unusual cellular elements in the red pulp.

Pancreas: The acinar tissue is intact and consists of pyramidal cells with more deeply basophilic basal portions and granular cytoplasm toward their apices. The islands of Langerhans are well differentiated and the epithelium is excellently preserved as

*We are indebted to Averill A. Liebow, M.D., Professor of Pathology, Yale University School of Medicine, New Haven, Connecticut, for this autopsy and report.

seen in the H and E stain. The epithelium of the ducts likewise appears to be intact.

Liver: In the large section of liver that is examined microscopically, there is no evidence of fibrosis nor of cellular infiltration. Those cells that are in the vicinity of the central vein have a granular cytoplasm. This suggests a rich content of glycogen. At the periphery of the lobules the cytoplasm is more homogenous. The nuclei of the hepatic and bile duct cells are well preserved throughout.

Adrenals: Three cortical layers can be distinguished. The cells of the fasciculate zone are larger and more coarsely granular than those of the other layers. There is not an excessive degree of fatty change. In most of the medullary cells there is an abundance of brown pigment. Here there is also a considerable infiltration of cells with the morphology of lymphocytes. A few smaller groups of these elements are seen also in the glomerular zone.

Kidneys: There is no evidence of damage to the nephrons. The glomeruli are well vascularized. The tubules have their typical characteristics at all levels and there is no evidence of necrosis. Small lymphoid accumulations are found focally in relation to the adventitial tissue of some of the larger veins. There are also a few groups of lymphocytes in small numbers along some of the distal convoluted and collecting tubules.

Gastro-intestinal Tract: In the stomach there are seen within the lamina propria considerable foci of lymphocytic and plasma cell infiltration. Masses of lymphocytes also penetrated the muscularis mucosae in some places to extend into the submucous layer. Here there are found some well defined lymphoid follicles with large germinal centers. The epithelium of the stomach is intact. In the small intestine lymphoid follicles are also plentiful even within the lamina propria. The epithelium, however, is intact. In one region in the ileum there is found in close association with the mucosal glands cross sections of what appear to be worms. There is no ulceration of the mucous membrane nor excessive cellular infiltration in the vicinity of these organisms. The colon also shows an intact mucous membrane and a few worms within the lumen.

Testes: The organ has the appearance of that of an immature child. The tubules are lined by columnar or stellate-shaped cells which stretch almost across the lumen. Among these, but in basal position, are larger cells with more spherical shape with both granular and eosinophilic cytoplasm. The latter probably represent spermatogonia of the immature testis while the former are probably the Sertoli cells. There is no evidence of spermatogenesis. Among the tubules are groups of deeply-stained small closely

crowded ovoid basophilic elements that appear to consist largely of a rather coarsely reticular nucleus. These are the interstitial cells. The basement membranes of the tubules are thin.

Thymus: The thymus has the typical architecture and shows no evidence of involution.

Central Nervous System: Sections from all portions of the brain are examined in Nissl preparations. The ganglion cells at all levels appear normal. The pia-arachnoid is thin and delicate and there is no gliosis nor cellular infiltration. The sections examined include the cortex at several levels, including the region of the Ammon's horn, the basal ganglions, the hypothalmus, the cerebellum and medulla.

Pituitary: The predominant cell type appears to be the neutrophilic, with eosinophilic elements next in relative incidence. There are also small acinar structures lined by tall columnar cells with ovoid nuclei and eosinophilic granular cytoplasm. These are found in all parts of the gland.

Bone Marrow: Smears and sections of marrow from the ribs show normally cellular tissue, with abundant megakaryocytes, and the usual proportion of red and white blood forming elements without shift to the left.

Conclusions

1) There is a local organizing peritonitis, presumed to be associated with repeated intraperitoneal injections.

2) There is a lymphoid and plasma cell infiltration of the stomach without ulcerative change.

3) There is a helminthic infestation of the lower intestinal tract.

4) The testes are underdeveloped (animal stated to be three years of age). Otherwise there are no significant changes in the gross and microscopic examination.

Discussion

For study of the individual compounds it would have been more exact if each compound had been given to a fresh group of monkeys. But from the viewpoint of cumulative toxicity it is significant that all three animals were given all three compounds with minor interruption for a period of ten months.

The tolerance that these animals demonstrated towards presumably therapeutic doses of the isonicotinylhydrazines enabled us to treat tuberculosis which developed spontaneously in another Macacus rhesus monkey that was the subject of a delicate and prolonged experiment. The monkey recovered, the experiment was completed and the animal was autopsied with findings which have been reported elsewhere.[5]

The lack of toxicity manifested by the general behavior, weight gain and maintainance of hemoglobin level has been confirmed by more elaborate studies (Tables II and III), and by the autopsy findings. Although some abnormalities were noted in the post mortem examination, it did not seem probable that these were due to the drugs. Additional autopsies and control studies are needed to elucidate these findings.

Although the isonicotinylhydrazines appear to have considerable toxicity when administered to rats and dogs[4] the fact that monkeys can tolerate these compounds in doses which are comparable with those used in the experimental chemotherapy of tuberculosis in lower animals[1-3] encouraged the rapid clinical

TABLE II

Studies on the Blood Serum and Urine of a Macacus Rhesus Monkey Treated Intermittently Over a Period of Ten Months with Isonicotinylhydrazines*

Serum Bilirubin	0.04 mg. per cent
Total Bilirubin	0.08 mg. per cent
Cephalin Flocculation	Negative in 48 hours
Thymol Turbidity	2.0 units
Thymol Flocculation	Negative
Alkaline Phosphatase	31.2 Bodansky units
Urine Urobilinogen	0.72/24 hours
Urine Bile	Negative

These are all normal, with the exception of Alkaline Phosphatase which is at least eight times above normal, at least as far as human standards are concerned. However, a number of other monkey bloods that we have examined have shown high values.

*We are indebted to Dr. Gerald Klatskin of the Yale University School of Medicine for these studies.

TABLE III

Studies on the Blood Cells and Bone Marrow of a Macacus Rhesus Monkey Treated Intermittently Over a Period of Ten Months with Isonicotinylhydrazines*

Red Blood Cells	3.85 million/mm.^{3}
Hemoglobin	12.2 Gm./100 cc.
Reticulocytes	0 per cent
Bone Marrow	20 per cent normoblasts Normal looking cellular marrow

*We are indebted to Dr. Allan Erslev of the Yale University School of Medicine for these studies.

evaluation of these drugs in human subjects. In fact the expansion of clinical studies with laboratory controls[5] and post mortem studies (not yet reported) relegate the findings described here to the realm of historical interest.[7-10]

SUMMARY

Macacus rhesus monkeys tolerate isonicotinylhydrazine and its glucosyl and isopropyl derivatives administered serially over prolonged periods and in doses sufficiently high to expect a possible antituberculous activity.

RESUMEN

El mono macacus rhesus tolera la isonicotylhidrazina y sus derivados glucosil e isopropil administrados en series durante periodos prolongados y en dosis suficientemente altas para esperar una posible acción antituberculosa.

RESUME

Les singes (Macacus rhesus) supportent l'isonicotinylhydrazine et ses dérivés glucosylique et isopropylique pendant des périodes d'adiministration prolongée, et à doses suffisamment élevées pour permettre une action antituberculeuse.

REFERENCES

1 Grunberg, E. and Schnitzer, R. J.: "Studies on the Activity of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice," *Quart. Bull.*, Sea View Hosp., 13:3, 1952.
2 Steenken, W., Jr. and Wolinsky, E.: "Antituberculous Properties of Hydrazines of Isonicotinic Acid," *Am. Rev. Tuberc.*, In press.
3 Grunberg, E., Leiwant, B., D'Ascensio, I. L. and Schnitzer, R. J.: "On the Lasting Protective Effect of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice," *Dis. of Chest*, 21: 369, 1952.
4 Benson, W. M., Stefko, P. L. and Roe, M. D.: "Pharmacological and Toxicological Observations of Hydrazine Derivatives of Isonicotinic Acid," *Am. Rev. Tuberc.*, In press.
5 Zieper, I. and Lewis, R. A.: "Tuberculosis in a Macacus Hhesus Treated with Isonicotinylhydrazine," *Quart. Bull.*, Sea View Hosp., 13:12, 1952.
6 Selikoff, I. J., Robitzek, E. H. and Ornstein, G. G.: "Toxicity of Hydrazine Derivatives of Isonicotinic Acid in the Chemotherapy of Human Tuberculosis," *Quart. Bull.*, Sea View Hosp., 13:17, 1952.
7 Robitzek, E. H., Selikoff, I. J. and Ornstein, G. G.: "Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid," *Quart. Bull.*, Sea View Hosp., 13:27, 1952.
8 Robitzek, E. H. and Selikoff, I. J.: "Hydrazine Derivatives of Isonicotinic Acid in the Treatment of Active Progressive Caseous-Pneumonic Tuberculosis," *Am. Rev. Tuberc.*, In press.
9 Selikoff, I. J. and Robitzek, E. H.: "Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid," *Dis. of Chest*, 21:385, 1952.
10 Bosworth, D. M., Wright, H. A. and Fielding, J. W.: "Marsilid in the Treatment of Tuberculosis Orthopedic Lesions," *Quart. Bull.*, Sea View Hosp., 13:52, 1952.

Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid

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Isonicotinic acid hydrazine, used as an intermediate in the preparation of the thiosemicarbazone of isonicotinaldehyde,[1] was found by Dr. R. J. Schnitzer and Dr. E. Grunberg of the Roche Chemotherapy Laboratories to exert a profound effect on the experimental tuberculosis of mice. Similar antituberculous activity was noted in Dr. Schnitzer's laboratory with several derivatives of isonicotinic acid hydrazide. The finding of this significant antituberculous chemotherapeutic effect in this new group of chemicals,[2,3a,b] plus the experimental indication of an adequate divergence of the chemotherapeutic and toxic ranges[4a,b] led to our investigations into this group of compounds.

We have investigated the toxicological and therapeutic properties of isonicotinic acid hydrazide, its glucosyl derivative (1-isonicotinic-2-glucosylhydrazine) and its isopropyl derivative (1-isonicotinyl-2-isopropylhydrazine).[5,6] Our clinical studies now extend beyond the seven month period. We have observed a marked chemotherapeutic effect in human tuberculosis with these hydrazine derivatives of isonicotinic acid. The antituberculous activity of this group of compounds is so definite and so significant clinically as to warrant a progress report of our presently continuing chemotherapeutic studies. Accumulating experience and multiplying observations will undoubtedly necessitate extension, amplification and modification of the tentative conclusions which are proposed here. Nevertheless, they are unlikely to alter the recognition of the necessity for inclusion of this new group of compounds into the therapy of human tuberculosis.

At the present time, 150 patients with various forms of pulmonary and/or extra-pulmonary tuberculosis have begun treatment with one or another of the compounds mentioned above. However, only 92 of these patients have been under observation for a sufficient period of time (4-15 weeks) to allow of adequate observation or analysis. The observations on these 92 patients

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therefore form the basis for this report and all comments will be limited to this group.

Material and Methods

All patients accepted for treatment in this study were carefully selected in conformity with the basic criterion that they were unlikely to respond to any possible standard therapeutic program. Each patient had active, progressive, extensive, bilateral caseous-pneumonic tuberculosis. In each, the prognosis was considered to be uniformly poor. Many were classified as "hopeless". In a few instances (six), therapeutic pneumothorax which successfully controlled the disease in one lung was allowed to continue, the therapy being directed primarily against the uncontrolled disease in the contralateral lung. These evaluations were based on careful review of history, study of all previous roentgenograms and analysis of clinical and laboratory findings. Patients were observed for an average of 9.15 months per patient on our own wards before institution of isonicotinic acid hydrazide therapy. All showing spontaneous improvement or improvement under any other means of therapy, were eliminated. Indeed, almost all (Table VI) had previously had other therapy. For example 76 patients had previously had streptomycin therapy with an average of 1.72 courses representing an average of 77.8 grams. Seventy-seven had had para-aminosalicylic acid therapy at an average dosage of 12 grams per day for an average period of 5.16 months. Thirty-eight had previously had artificial pneumothorax therapy and 14 had had pneumoperitoneum therapy which had failed to control the disease. Surgical procedures had been performed on eight patients; these included both excisional and collapse measures.

Careful pre-therapy studies and baseline evaluations were performed for each patient conforming to the above criteria. These studies included complete blood counts, urine studies, cephalin flocculation tests, sedimentation rates, new roentgenograms, and other biochemical and electrocardiographic investigations. Special studies were conducted where indicated. In instances wherein additional opinion was desired, consultation with members of our consulting services was obtained. Each patient was then examined and questioned in order to achieve a base-line estimate of a variety of signs, symptoms and findings for later reference. Records were obtained as to the intensity and character of cough, the amount and character of the expectoration, the weight, the degree of general toxicity represented in plusses, the appetite graded as good, fair, poor and bad, the temperature, the sense of strength, energy and well-being also subjectively graded and given evaluations. At this interview, psychological features were considered

to insure selection of patients who would persevere and cooperate in the study.

Every patient selected had sputum consistently positive for acid-fast bacilli. All showed cavitary, caseous-pneumonic pulmonary tuberculosis on pre-therapy roentgenogram. In none did any other modality or medication offer hope of significant therapeutic benefit. These patients had, so to speak, "reached the end of the therapeutic road."

Pre-Therapy Status of Patients

The full picture of the patient's pre-therapy status only becomes apparent when all of the above observations have been correlated. While the roentgenogram may indicate considerable similarity in the disease processes in each of two patients, the systemic effects may only be reflected by the clinical observations. Thus, two patients with equal parenchymal destruction may anticipate sharp differences in prognosis based on a number of ill-defined variables including underlying pathology, tissue sensitivity and allergic response. The active, exudative, caseous-pneumonic disease with fever, toxicity, anorexia and weight loss augers a serious outlook. An identical degree of pulmonary destruction with fibroproductive, indolent disease, unassociated with severe systemic manifestations, prognosticates a somewhat different course. In order to obviate these differences, therefore, patients were deliberately selected who exhibited each principal type of disease in all its variations and nuances. It was felt that in this way a total evaluation of the chemotherapeutic efficacy of the drugs under study could be obtained. This dichotomy was deliberate and necessary. Its extent can best be appreciated by an analysis of the pre-therapy status of the patients in this group.

Fever: Forty-four of the 92 patients under study had fever ranging from 100 to 105 degrees F. during the pre-therapy observation period. No patient was included in the febrile group unless the fever was found to be persistent for at least a one-month period prior to therapy. It should be noted that 10 patients suffered continuous fever of from 102 to 105 degrees F. daily before institution of therapy. Almost all of these patients were simultaneously toxic and exhibited weight loss and anorexia. All temperatures were taken rectally and only maximum temperatures were recorded (Table I).

Appetite: As a rule appetite was poor in the group under study, although this was not universally true (Table II). Appetites were graded, as noted above, on an arbitrary scale, utilizing the patient's impressions, the observations of the nursing staff and our own evaluation. A comparison was made in each case with the

patient's appetite before becoming ill with tuberculosis and this was used as a baseline.

Toxicity: Evaluation of this symptom is partially subjective and was obtained from the patient's statements, the observations of the nursing staff and our own clinical impressions as to appearance, color and turgor of skin, hydration and response to stimuli.

TABLE I

Temperature Range Before Onset of Therapy
Range from One to Five Months

Temperature	Number of Patients
100°	16
101°-102°	18
103°-105°	10
TOTAL	44

TABLE II

Appetite During Pre-Therapy Period

Appetite	Number of Patients
Good	14
Fair	17
Poor	52
Bad	9
TOTAL	92

TABLE III

Toxicity in Patients During Pre-Therapy Period of Observation

Toxicity	Number of Patients
Zero	20
One plus	30
Two plus	24
Three plus	11
Four plus	7
TOTAL	92

TABLE IV

Weight Loss (Pounds) in Pre-Therapy Course

Weight Loss	Number of Patients
0-9 Pounds	22
10-19 Pounds	26
20-29 Pounds	18
30-39 Pounds	15
40-49 Pounds	6
50-59 Pounds	4
60-69 Pounds	0
70-79 Pounds	1
TOTAL	92

TABLE V

Personal Status of Patients

Range (Years)	Number of Patients
A G E	
10-19	7
20-29	19
30-39	19
40-49	23
50-59	17
60-80	7
TOTAL	92
S E X	
Male	54
Female	38
TOTAL	92
C O L O R	
White	34
Negro	49
Puerto Rican	8
Chinese	1
TOTAL	92

Table III is an index of the status of our group at the onset of therapy.

Weight Loss: Every patient accepted for treatment in this study was below normal weight, often considerably below normal weight. Many were emaciated, especially several of the almost moribund patients. One patient weighed as little as 56 pounds and only the so-called "good chronics" had normal robust appearance. Few patients were stationary at the time of onset of therapy—most showed progressive decline. Table IV indicates the weight status of the patients in this investigation during their pre-therapy course.

Personal Status of the Patients: No selection was attempted on the basis of age, sex, race or color. Inevitably preponderances within one or another of the groups occurred. The ages ranged from 15 to 80 with an average of 40 years. Table V represents an

TABLE VI
Previous Therapy

A. *Streptomycin Therapy:*

Previously treated with streptomycin		76 patients
	Number of Patients	
1 course	39	
2 courses	23	
3 courses	13	
4 courses	0	
5 courses	1	
Average number of courses		1.72
Average total streptomycin (Gm.)		77.8

B. *Para-aminosalicylic Acid**

Previously treated with PAS	77 patients
Average duration of therapy	5.16 months

	Number of Patients
C. *Pneumothorax therapy*	38
D. *Pneumoperitoneum therapy*	14
E. *Surgical (Collapse, Excisional, etc.)*	8
F. *Thiosemicarbazone*	1
G. *Diasone*	1

*Usually simultaneous with Streptomycin.

analysis of this data. There were 54 males and 38 females. Forty-nine patients were Negro, 34 were white, eight were Puerto Rican and one was Chinese.

The known duration of the disease also varied. The range was from six months to 23 years with an average of 38 months. Of more importance perhaps, was the duration of the present acute illness. This averaged 1¼ years: 64 patients were ill for one year or less.

Previous Therapy: As noted above, almost all patients have had previous trial of other forms of therapy in addition to bedrest. a) *Streptomycin:* Seventy-six of the 92 patients in this study had had previous trials of streptomycin. b) *Para-aminosalicylic acid:* Seventy-seven had had para-aminosalicylic acid therapy for an average period of 5.16 months. c) Thirty-eight had had previous *pneumothorax*. d) *Pneumoperitoneum therapy:* Fourteen had had previous pneumoperitoneum therapy. e) *Surgical therapy:* Eight had had prior surgical collapse or excision. One had had two courses of thiosemicarbazone, one had had Diasone. This data is summarized in Table VI.

TABLE VII

Cough and Expectoration Before Therapy

	Number of Patients
Zero	1
One plus	29
Two plus	35
Three plus	25
Four plus	2
TOTAL	92

TABLE VIII

Bacteriological Sputum Status Before Onset of Therapy

	Number of Patients
Positive on Unconcentrated Smear—Gaffky VI - X	53
Positive on Unconcentrated Smear—Gaffky I - V	34
Positive on Concentrated Smear	5
TOTAL	92

TABLE IX: Pre-Therapy Classification of 92 Patients

GROUPS	Exudative	Productive	Caseous-Pneumonic	Exudative Caseous-Pneumonic	Exudative Productive	Productive Caseous-Pneumonic	All Three	Recent Spread	Progressive	Stationary	Regressive
Group I—Marsilid 2 mgs./K. from 10/2/51 4 mgs./K. from 11/20/51 15 patients			1	3		7	4	4	3	8	
Group II—Marsilid 2 mgs./K. from 10/15/51 4 mgs./K. from 11/20/51 6 patients				2	2	1	1	1	2	3	
Group III—Marsilid 2 mgs./K. from 10/25/51 4 mgs./K. from 11/20/51 7 patients			2	1	1	3			4	3	
Group IV—Marsilid 4 mgs./K. from 11/15/51 28 patients		1	1	6	1	14	5	1	5	21	1
Group V—Marsilid 4 mgs./K. from 11/23/51 16 patients			7	5		2	2		8	8	
Group VI—Marsilid 10 mgs./K. from 12/6/51 10 patients			1	6		2	1	3	7		
Group VII—Rimifon 2 mgs./K. from 12/17/51 4 mgs./K. from 12/24/51 10 patients			1	5		4		2	6	2	
TOTALS		1	13	28	4	33	13	11	35	45	1
		— — — — — — 92 PATIENTS — — — — — —						— — 92 PATIENTS — —			

In no instance did this previous therapy control the patient's disease. In every case the disease was either stationary or progressive.

Cough and Expectoration: Although evaluation of cough is largely subjective, it was graded from 1 to 4+ through estimations made by the patient, the nursing staff and ourselves. Expectoration could be quantitated. The sputum cup in use at Sea View Hospital is an 8 ounce receptacle. The 24 hour sputum specimen was measured and graded as follows: ½ cup (1-4 oz.) = +; ½-1 cup (4-8 oz.) = ++; 1-2 cups (8-16 oz.) = +++; over 16 oz. per day = ++++. Cough and expectoration are tabulated in Table VII.

Bacteriology of Sputum: Every patient accepted for therapy in this investigation had positive sputum. Almost all were positive on unconcentrated smear. As noted in Table VIII, of the 92 patients, 53 were repeatedly positive in the high Gaffky range on unconcentrated smear. Thirty-four were positive in the lower Gaffky ranges (from Gaffky I to Gaffky V). A few (five) were only positive on concentrated or gastric specimens.

Pre-therapy Course: Evaluation of the pre-therapy course was principally radiological. As illustrated in Table IX, 35 of the 92 patients had progressive radiological deterioration as evidenced by spreading exudate, increasing cavity size, or new cavities. Another 11 showed evidence of recent spread on roentgenograms. Forty-five showed relatively stable recent roentgenograms. In general, this evaluation agreed with that obtained clinically.

Roentgenographic Status and Classification: A duality of classification was utilized in this study. The first, suggested by the National Tuberculosis Association, showed that 69 were far-advanced and 23 were moderately advanced. None was minimal. Supplementing this classification and in order to illustrate the nature of the underlying pathology, we utilized the classification of Ornstein et al.,[7] which has been found to be of exceptional clinical value at our institution. Our findings are tabulated in Table IX.

Non-Tuberculous Disease: Twenty patients in this series suffered from a variety of diseases unrelated to the pulmonary tuberculosis. These included latent or active lues, alcoholism, asthma, sickle cell anemia, chronic otitis media, previous psychosis, recurrent urticaria and probable amyloidosis.

Extrapulmonary Tuberculosis: Extrapulmonary disease was present in 17 patients. In three, there was quiescent genito-urinary or perirectal tuberculosis, two suffered from tuberculous otitis media, 10 had active tuberculous laryngitis, one had severe empyema and broncho-pleural fistula and one had a marked tuberculous glossitis.

Plan of Study

No other therapeutic agent or treatment was given to any patient once he was accepted for therapy. This rule was absolute with the exception of successful unilateral pneumothoraces in whom the contralateral lung was uncontrolled and required therapy. Not even vitamins were allowed. Where pneumoperitoneum had been given, refills were stopped before the onset of therapy. Since complete reabsorption of abdominal air is often slow, many of the patients had residual air during the first few weeks of therapy. Similarly, total reabsorption of pneumothoraces was not awaited before institution of therapy. Placebos were not used since it was felt that all evaluations of success or failure of therapy was to be principally by objective measurement. Clinical symptomatology, while instructive and valuable, must correlate with rather than substitute for overt evidence of chemotherapeutic effect. No changes were made in the daily routines of these patients. The nursing staff was instructed that no special attention was to be given patients on therapy; if they were unconvinced of the necessity for bedrest and refused to follow the rules, they were to be allowed to continue their previous habits. Similarly, no special food or nursing care was given. All patients in our hospital are allowed to eat all the food they desire. Ambulatory patients continued ambulatory and ward routine was maintained. Patients were weighed once weekly; sputum examinations were done weekly and roentgenograms were taken monthly. Laboratory studies such as hematological examinations, cephalin flocculation tests and urine analyses were done weekly at first, then bi-weekly and finally, with the paucity of positive abnormal findings, triweekly or monthly. Anti-tussive drugs were allowed although, as will be seen below, they rapidly became unnecessary and soon disappeared from medication order sheets.

Medication was given in various dosage ranges (see below) orally, three times a day after meals. All doses were approximate. Marsilid was available in 50 mg. scored tablets and dosage was exact to the half tablet. Rimifon was available in 25 mg. scored tablets and was similarly utilized. In one instance, during the early stages of treatment of a patient with an extensive tuberculous ulcer of the tongue, there was pain on administration of the tablet so that it had to be crushed and given in liquid. No special storage precautions were taken and the preparation appeared stable. There was no clinical variation observable from lot to lot. There was no necessity for rectal, subcutaneous, intravenous or intramuscular administration of the drug. No patients objected to the drugs on the basis of taste or local effect, nor were objections advanced because of gastrointestinal irritation. There

were no instances of direct irritative, allergic or dermatologic reactions among those handling the drug.

Once begun, in almost every case, administration was continuous. Dosages per kilo were variable although the total daily intake was unchanged. This was the result of rapid weight gain which occasionally added considerably to the total body weight automatically, thereby, reducing the per kilo dosage. We do not believe that this introduces significant error. Tablets were of the plain, compressed variety; no patient, upon questioning, volunteered having passed unassimilated ones in the stool. This corresponds to the observations[8] that absorption of both the isonicotinic acid hydrazine and its isopropyl derivative is rapid, with high initial blood levels being found at least within the first hour after administration. This corresponds, too, to our observation that side effects, when observed, are commonly experienced during the first one and one half hours after administration of the drug. This plan of administration is a tentative one and may be modified on the basis of studies now being conducted.

Dosages: Details with regard to dosage levels will be given more completely in the paragraphs analyzing the separation into groups of the patients in this study. Our overall dosage levels have ranged from 2 to 4 mg./K. of body weight of isonicotinic acid hydrazide and from 2 to 10 mg./K. of body weight of its isopropyl derivative.

Plan of Therapy

In order to allow study of the chemotherapeutic effects at varying dosage levels and to permit laboratory and clinical toxicological investigations within the same levels, patients were begun on therapy in consecutive groups. Dosages varied in consecutive groups according to the experiences gained with the preceding ones. Thus, for example, no groups of patients were added at the 4 mg. level of the isopropyl derivative until it was determined that no serious toxicological effects were noted at the 2 mg. level. Similarly, each group was continued on a given dosage level for a sufficient period to allow comparative observations with other levels on toxicity, temperature, weight, cough, etc. Thus a quantitative evaluation was sought in order to establish tentative estimations of minimal, maximal, and optimum dosage levels for therapeutic purposes. Apart from these considerations, the groups were not otherwise separated. There was no attempt at individualization of the dosage or drug. There was no selection of patients into each group and all were approximately the same, insofar as type, extent and severity of disease was concerned. Each group received only one drug although dosage levels were varied as specified below.

Our present study, organized primarily as a therapeutic investigation and only secondarily toxicological, began on October 2, 1951. At this time, a group of 17 patients was started on therapy with 1-isonicotinyl-2-isopropyl hydrazine (Marsilid) at a dosage level of 2 mg./K. This group continued at this dosage level until November 20, 1951, when it was adjudged to have given sufficient information regarding the therapeutic efficacy and toxicological side effects at the 2 mg. dosage level and the dosage level was increased to 4 mg./K. It has continued on this level since. On October 15, 1951 a group of six patients began therapy at 2 mg./K. of Marsilid and on October 25, 1951 an additional group of seven patients was added. These latter two groups were also increased to 4 mg./K. on November 20, 1951. On November 15, 1951 a group of 29 patients was begun on Marsilid therapy at a dosage level of 4 mg./K. and this entire group has continued at this dosage level since. On November 23 an additional group of 17 patients instituted therapy at the same dosage level of the same drug and this group has also continued as initiated. A further group of 10 patients was begun on Marsilid therapy on December 6, 1951 but this time a dosage level of 10 mg./K. was utilized. This group has continued at this level since. It was felt that these six groups would provide sufficient toxicological data to supplement that which had been obtained with the isonicotinic acid hydrazide and its glucosyl derivative during the earlier studies.[5] Therefore, we returned to the study of isonicotinic acid hydrazide (Rimifon) and on December 17, 1951 instituted therapy in a group of 10 patients at a dosage level of 2 mg./K. This, after one week, was increased to 4 mg./K. This group has continued at this dosage level since.

Several patients who began therapy in the above groups have been eliminated from our therapeutic calculations. Two who began therapy in the first group were dropped, one (J. A.), because of death after 10 days of treatment due to massive hemoptysis. Hemorrhage had been present before the onset of therapy and continued through therapy. During the brief period in which he had been taking Marsilid there was definite clinical improvement in his laryngeal symptoms, but since no other reliable data were obtained, further reference to his status will not be included. The second patient (E. J.) showed marked clinical improvement and sputum conversion while under treatment but is not being considered from the therapeutic point of view because of the fact that, due to persistent hemoptysis a hemostatic pneumothorax was induced and has been continued therapeutically. Although it is unlikely that this pneumothorax independently controlled this patient's rapidly deteriorating course, this possibility cannot

be eliminated and the patient is therefore not tabulated in this therapeutic study. One patient in group V. (T. W.) was only under treatment for approximately two weeks and then was discharged from the hospital for disciplinary reasons although in that brief period her sputum was converted to negative and she showed evidence of marked symptomatic clinical improvement. Nevertheless, her course of observation was too short for accurate evaluation and no further mention in the therapeutic calculations will be made. Finally, one patient in group IV. died after his fifth week of therapy. Autopsy revealed bronchogenic carcinoma with penetration into the mediastinum and oesophagus, with death due to shock. This patient, too, is not included in any therapeutic calculation. All data on all other patients have been included in the tabulations to follow.

Although additional groups of patients have begun therapy with these compounds at varying dosage levels, duration of observation has been too short for adequate evaluation and our experience with these groups will be reported later. At present, there are under treatment with isonicotinic acid hydrazide and its derivatives approximately 150 patients with pulmonary tuberculosis as well as others with tuberculosis of bone and joint, genito-urinary tract and meninges. Other patients demonstrating special problems associated with our pediatric, otolaryngological and other specialized services are also under treatment.

Observations on the Therapeutic Efficacy of Isonicotinic Acid Hydrazide and Its Isopropyl Derivative, 1-isonicotinyl-2-isopropyl hydrazine

Our investigations indicate that isonicotinic acid hydrazide and its derivatives form a highly effective group of compounds for the treatment of human tuberculosis. Although much observation and study will be required before the limitations and scope of the chemotherapeutic effectiveness of this new group of compounds will be defined, their therapeutic effectiveness is so marked that observations to date are worthy of early record.

We find it easier to describe the scope than to define the limitations of these drugs at this time. Of the 92 patients described in this investigation we have not seen one who did not exhibit, in greater or lesser degree, therapeutic response to the drug used for treatment. This included patients treated with either derivative and included patients in every dosage range. Obviously, therefore, no definitive statements are available on many of our observations. This unexpected range of therapeutic efficacy has extended over all ages, both sexes, all races; it has included each variety of pulmonary pathological lesion and classification and has em-

braced every clinical status ranging from the long-standing indolent, "chronic" disease to the acutely active, progressive, exudative, rapidly spreading, highly toxic, caseous-pneumonic disease.

This indiscriminate therapeutic activity of this new group of compounds simultaneously makes necessary more varied and extensive review of the results of such therapy.

Systemic Response to Chemotherapy with Isonicotinic Acid Hydrazide and Its Derivatives

For the physician, the most dramatic demonstration of the effect of treatment of human tuberculosis with isonicotinic acid hydrazide or its derivatives, lies in the rapid, marked and thorough alleviation of the systemic effects of tuberculous infection. This was particularly striking among these patients, since they were specially selected for their poor condition. They were, as a group, progressively deteriorating and with uniformly bad prognosis. Therefore, reversal of their course was all the more dramatically revealing.

Effect on Temperature: One of the earliest and most striking evidences of therapeutic efficacy of the drugs under consideration appeared in the temperature record. Of the 92 patients studied, 44 suffered from greater or lesser degree of fever before the onset of therapy. In every case, without exception, fever was rapidly eliminated. This usually took place within one week; occasionally in two weeks; rarely longer. Not infrequently, it took place in two or three days, and with higher dosages it occasionally occurred on the first day. Usually, the decline was one of lysis over a period of several days. In some instances, it was precipitous, with a sudden drop on the day of initiation of therapy or the subsequent day, one or two brief small spikes thereafter, and a subsequent afebrile course. At the present writing, there is not a single patient under therapy with an elevated temperature. During the earlier phases of this investigation, as we noted this marked effect on fever, we considered the possibility of a non-specific antipyretic effect. We soon observed, however, that loss of fever was correlated with other systemic improvement and, further, that the temperature drop was persistent even after discontinuance of medication. Thus, this observation is rather an indication and an index of the systemic response to the therapeutic activity of this drug. We did notice that when temperature was due to empyema, it responded more slowly and more poorly. Here too, however, the complete response was obtained. In one instance a patient with secondary non-specific pulmonary infection, with active, extensive, pulmonary disease, failed to experience temperature drop despite Marsilid therapy until a brief exhibition of

penicillin and terramycin effectively controlled the accompanying non-specific infection. In a number of instances brief, minimal elevations of temperature occurred during the course of therapy in patients previously rendered afebrile, due to intercurrent respiratory infection. These were rapidly overcome with the usual therapeutic measures. Incidentally, we are now able to distinguish temperature elevations due to non-specific respiratory infections complicating pulmonary tuberculosis. Every case with an interval rise in temperature during therapy was found to have an intercurrent non-specific respiratory infection. Previous to the utilization of isonicotinic acid hydrazide therapy, this differentiation was difficult and often the cause for concern lest a spread, or other extension of disease, had accurred.

A case which exemplifies this significant effect on fever is reported in the following section. Others have been reported elsewhere.[9] These are not unusual and similar findings have been obtained by us in each febrile case treated in this group.

Case Report No. 1: E.M.—Chart No. 36792. This 22 year old colored male was admitted to Sea View Hospital on October 11, 1951. In June of 1951 he had the onset of symptoms of acute pulmonary tuberculosis, and his disease progressed. During the months before admission he rapidly lost weight from his normal of 195 pounds to 144 pounds. Beginning in July 1951, he was treated with a 50 day course of streptomycin, at 1 Gm. daily, concommitant with para-aminosalicylic acid. This failed to materially alter his course. When seen by us, he was severely ill. He had been continuously febrile for over five months, with fever ranging from 102 to 104 degrees F. He was markedly toxic and bedridden because of weakness. There was only moderate cough and expectoration and sputum was persistently positive on direct smear. Peripheral neuropathy, considered to be a vitamin deficiency, responded poorly to vitamin therapy. Roentgenograms showed far-advanced bilateral caseous-pneumonic tuberculosis with a huge cavity in the upper half of the left lung (Fig. 1a).

Marsilid therapy was begun on November 15, 1951, at 4 mg./K. His temperature partially subsided by the first week and by the second week of therapy it was completely normal (Fig. 1b). Simultaneously, cough and expectoration ceased and evidences of toxicity disappeared. His appetite became insatiable and he rapidly regained strength. Within nine weeks he had regained 53 pounds (Fig. 1c). On the first three direct examinations of his sputum, following institution of Marsilid therapy, tubercle bacilli were found. The last five examinations, subsequent to December 10, 1951, have been consistently negative. Roentgenographic examination on January 8, 1952 showed considerable reabsorption of the exudative disease originally present, although the giant cavity is still noted (Fig. 1d). He continues on Marsilid therapy.

Effect on Toxicity: Isonicotinic acid hydrazide and its derivatives demonstrate a dramatic effect on the toxicity resulting from the systemic effects of tuberculosis. While question as to the mechanism of such action might be raised, that such effect is profound

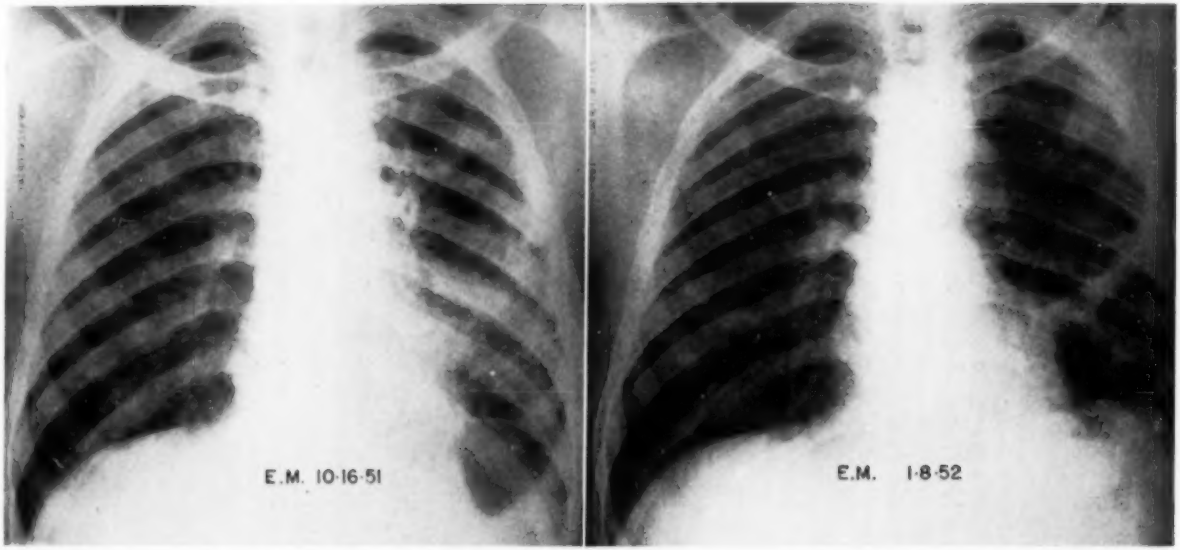

FIGURE 1a FIGURE 1d

FIGURE 1a, CASE 1: E.M. X-ray film of October 16, 1951 shows extensive bilateral exudate and extensive left upper lobe cavitation.—FIGURE 1d, CASE 1: E.M. X-ray film of January 8, 1952 shows considerable clearing of exudate. The cavitation persists.

and rapid is indubitable. Indeed, during the early weeks of this study, when wards were "mixed" (containing patiets both taking therapy and those not taking therapy), it was possible to determine, merely on the basis of presence and absence of toxicity (appearance, energy, skin turgor, behaviour, etc.) which patients had been taking therapy and which had not. This effect on

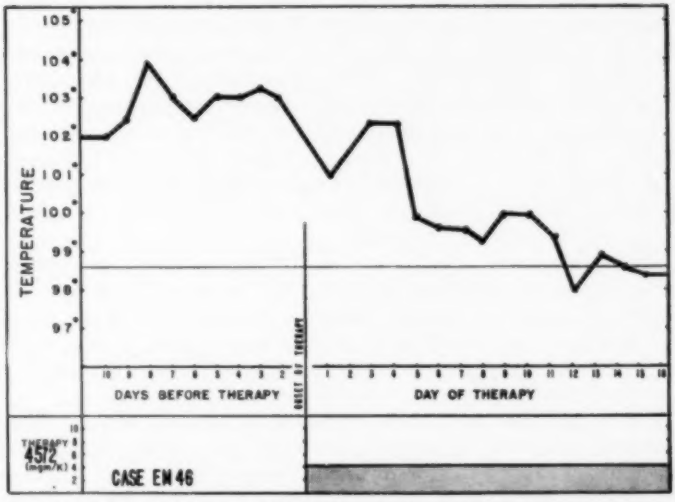

FIGURE 1b, CASE 1: E.M. The temperature decline is complete within the second week.

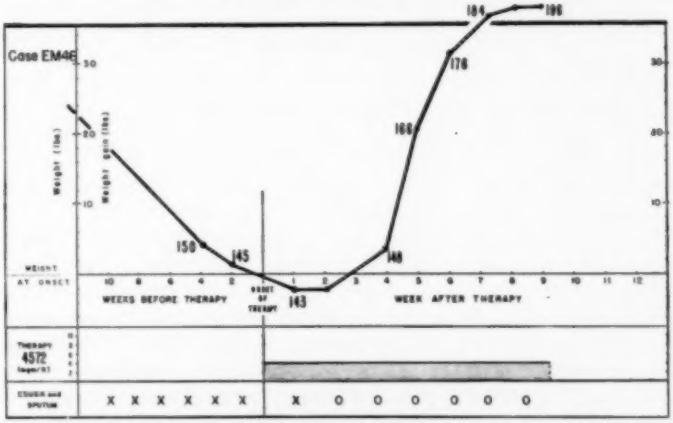

FIGURE 1c, CASE 1: E.M. The extraordinary weight gain is well illustrated by this graph.

toxicity appeared within the first week in most cases. Occasionally subjective observations in this regard were volunteered by patients on the second or third day. In a few instances it was not appreciated for several weeks. No patient now on treatment in the group here reported has residual evidence of toxicity.

The earliest improvement came in the general sense of well-being. This usually correlated with and often preceded drop in temperature but not necessarily so. It was associated with relief of anorexia. It often accompanied return of skin turgor and color to normalcy, although skin restorations occasionally preceded it. Weight gain and return of strength followed rapidly so that most bedridden patients became ambulatory by the second or third week of treatment. All patients are now ambulatory. Strength and energy rapidly returned; lethargy disappeared. The patients exhibited renewed vigor and indeed this occasionally served to introduce disciplinary problems.

Eight among the 38 females in the series were amenorrheic, seven resumed menstruation after the onset of therapy. The amenorrhea had previously been of variable duration, up to two years, and is considered to be an accurate index of the extent of toxicity of these patients. The resumption usually occurred in the first month of therapy, occasionally in the second.

Before the onset of therapy a number of patients had exhibited evidence of severe vitamin deficiency of the B complex group; these had persisted despite intensive vitamin therapy. It has been shown that such resistant avitaminosis is usually dependent upon the activity and progression of the underlying tuberculosis with its systemic and metabolic disturbances.[10] These observations were confirmed during the pre-therapy period. Peripheral neuropathy and cheilosis and glossitis were resistant to all vitamin therapy so long as the toxic systemic effects remained unchecked. However, when therapy was instituted, these evidences of avitaminosis rapidly disappeared, usually within two to three weeks. It occurred in the absence of supplementary vitamin therapy. This is a significant commentary on the readaptive powers of the organism once the toxic metabolic effects have been eliminated.

Effects on Appetite: Pre-therapy anorexia was alleviated in every patient save one. The appetite recovery, once therapy was instituted, was of remarkable degree. The only term adequately descriptive is "insatiable". Consumption of 11 eggs for breakfast, four, five and six helpings of cereal, the formation of "medicine lines" composed of patients who were on therapy and were cueing up for second, third and fourth helpings at the food dispensing truck, are not unusual. Our dietary division has informed us that at least 50 per cent more food is now being consumed on the wards

being utilized for this study, and the supply of milk has been doubled. Our chief dietician, Mrs. Louise Curtis McCue, has calculated that the average daily intake now approximates 5,000 calories, containing approximately 180 Gm. of protein. No special food has been given and no special preparation allowed. Patients are simply given all they want to eat.

This relief of anorexia was prompt. It coincided with loss of toxicity and temperature drop, although there was no uniformity in the order of occurrence since return of appetite occasionally preceded the temperature decline. This remarkable recovery is an accurate index of the profound ameliorating effects of isonicotinic acid hydrazide and its derivatives on the systemic, toxic effects of tuberculosis seemingly quite apart from any hypothetical appetite stimulating properties. All doses were given after meals. Studies to date[8] in our patients indicate that there is rapid absorption of the drug with blood level peaks during or at the first hour after ingestion and with relatively rapid decline during the succeeding hours; lower levels are present in the blood prior to the succeeding meal. Moreover, no drug at all, or extremely small amounts were present in the blood before breakfast, no medication having been given since the preceding night. Therefore, the excellent appetites exhibited at breakfast time could hardly be ascribed to immediate specific action of the drugs apart from that on the systemic toxicity of tuberculosis.

Weight Gain: Although the weight of the patient, or the direction of its change is not necessarily an accurate reflection of the status of the underlying pulmonary disease, it is frequently a sensitive index of the systemic effect of the tuberculous process. Weight loss reflects the inexorable derangement of the metabolic status of the patient through the systemic effects of the infectious process. It is an index, too, of the patient's entire metabolic economy including the catabolic effects on the dynamic pool of protein metabolism, possibly through sub-clinical hepatic damage, endocrine imbalance and the other systemic causes for constitutional symptomatology. Thus, observation of the weight curve of the patient under treatment is a valuable guide to the evaluation of the chemotherapeutic effectiveness of any anti-tuberculosis compound.

Our experiences in this investigation may be summarized with the statement that therapy with this new group of compounds causes immediate cessation of weight loss and rapid reversal of the weight curve in almost every patient. This included all ages, both sexes, and every type of disease. It was as true of highly toxic, febrile patients undergoing rapid deterioration and steady weight

FIGURE 2a FIGURE 2b FIGURE 2d

FIGURE 2a, CASE 2: M.N. X-ray film of March 11, 1949 showing chronic bilateral upper lobe cavitation of long duration. FIGURE 2b, CASE 2: M.N. X-ray film of September 21, 1951 showing little change of chronic disease during previous two and one-half years.—FIGURE 2d, CASE 2: M.N. X-ray film of January 11, 1952 shows diminution of cavities in both upper lobes after three months of therapy. These had previously shown no change over long period of time on serial films.

loss as in the so-called "good chronics" whose weight curves had been consistently stable over a period of years.

In those patients in whom the pre-therapy period of observation indicated continuous weight loss of from six to 12 months, the loss ceased almost immediately upon onset of therapy. Usually the second week showed no further weight loss, although a pound or two may still have been dropped during the first week. The third week usually showed the first significant ascension. Thereafter continuous weight gain becomes the rule and, in our experience to date, has continued without interruption as long as the patient continues on therapy. The effect is more gradual and of lesser degree in patients beginning treatment at or near their expected normal. Nevertheless, here too, the weight curve begins its ascent within the second or third week of therapy and continues steadily. The extent of weight gain has been remarkable. Except for four patients in whom weight gain was delayed (two because of dental problems, one because of pulmonary insufficiency due to advanced emphysema, and one whose recovery was retarded by an active tuberculous empyema with broncho-pleural fistula) the increases averaged 15 to 50 per cent of the patient's initial body weight. Our data indicate that the weight gain is probably at the maximum to be expected from the metabolic limitations of the human organism. Some patients exhibited a steady weight gain of 3 to 5 pounds every single week; others were more sporadic with occasional gains of 7 to 10 pounds in one week. This weight gain coincides with disappearance of toxicity and resurgence of appetite. Almost every patient who has been on therapy for from

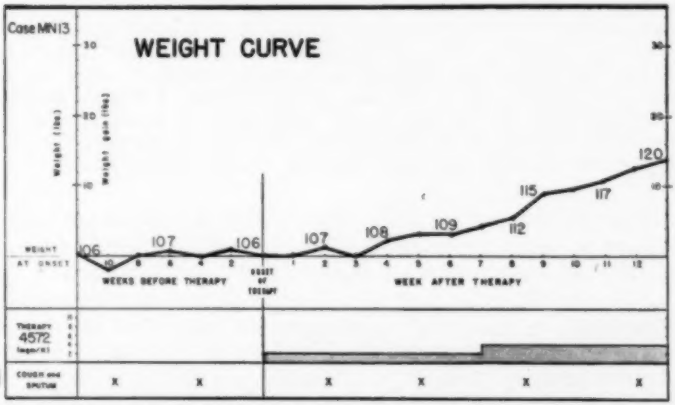

FIGURE 2c, CASE 2: M.N. Gradual weight gain even in long-standing chronic disease is illustrated by this graph.

eight to 15 weeks is now at or above normal weight. It has been revealing to note how rapidly and how completely human metabolism can readjust itself to correct assimilation and utilization of food once the deranging effects of the toxic disease process have been removed.

Our observation in this investigation also exemplify the subclinical but nevertheless important metabolic disturbances attendant upon longstanding chronic infection which may give little or no overt constitutional symptomatology. Almost 25 per cent of the patients under study were in the so-called far-advanced "good chronic" group. Yet, this group, too, showed the same response with regard to weight as did those patients with more active disease. Each of these patients gained weight, albeit somewhat more slowly and to lesser degree. A case illustrating weight gain even in chronic longstanding disease follows.

Case Report No. 2: M.N., No. 18182. This 58 year old white male had suffered from pulmonary tuberculosis since 1939. In that year an ineffectual pneumothorax was attempted but was soon abandoned. He had subsequently been treated conservatively. In 1950 a brief course of para-aminosalicylic acid was abandoned because of gastrointestinal upset. Observation at this hospital since 1949 failed to reveal any changes in his unspectacular chronic course. Figure 2a is a roentgenogram taken on March 11, 1949 showing bilateral upper lobe cavitation. On September 21, 1951, shortly before starting therapy, the chest film (Fig. 2b) showed no changes from the findings of two years before. At this time there was a moderate cough, productive of approximately 8 ounces of mucopurulent sputum with all examinations highly positive. His appetite was poor and although ambulatory, his energy was deficient. The temperature ranged around 98 degrees F. and there was no toxicity. His weight for 12 years before therapy remained at 105 pounds. He began Marsilid therapy on October 2, 1951 at a daily dose of 2 mg./K. This was raised on November 20, to 4 mg./K. Almost imperceptibly at first and coincident with improvement in his increasing sense of well-being and appetite he gained five pounds between October 2 and November 19, 1951. Weight gain accelerated on the larger dose and on January 14, 1952 he weighed 122 pounds (Fig. 2c). His sputum has diminished but is still positive. He feels well, is strong and his latest film on January 11, 1952 shows distinct diminution in cavity size bilaterally (Fig. 2d). He remains under treatment.

Of the 92 patients in this series, there has been an average weight gain of 18 pounds in an average of nine weeks. Considering those patients who have had a minimum of eight weeks of therapy, we find that 71 patients gained an average of 21 pounds in an average of 10 weeks, or approximately 2 pounds per week. With the dosage ranges utilized in this study, weight gain occurred at all dosage levels of therapy. However, it is smaller and slower in the lower dosage ranges. This effect of dosage was apparent even in the same patients. Thus, 17 patients were begun on Marsilid therapy

at a level of 2 mg./K. and were increased after seven weeks of therapy to 4 mg./K. The weight curve of this group is reproduced in Figure 3, showing that the rate of gain is increased with higher ranges. Similarly, as demonstrated by this graph, if we compare the rate of weight gain of those patients receiving 4 mg./K. and those receiving 2 mg./K. we find there is an even more rapid initial weight gain at the higher dosage level. Data are as yet inadequate regarding the effects of higher dosage ranges with

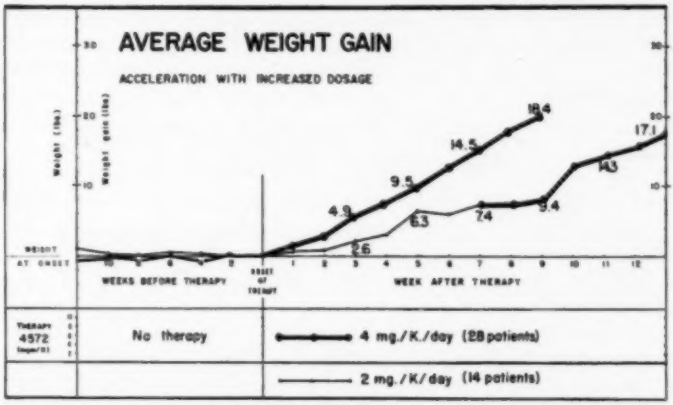

FIGURE 3: Composite graphs of patients on 2 mg. and 4 mg./K. of Marsilid. Weight gain occurs with the former dose but is accelerated on doubling the dose. Comparison shows that a group beginning on the higher dosage level gained weight more rapidly.

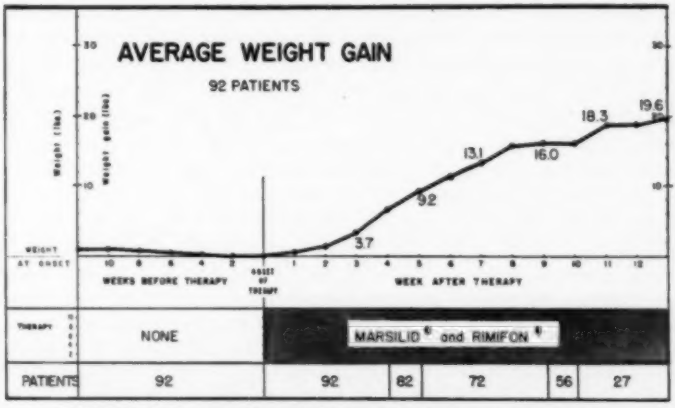

FIGURE 4: Composite weight graph of all patients taking Marsilid and Rimifon.

Rimifon therapy. Figure 4 is a similar graph representing the combined curve of all patients in this series.

Weight gain has been so spectacular that at first we were concerned lest water retention be playing some role in its development. However, in every case in which extreme increase occurred, it always coincided with enormous appetite and intake of food. We have not observed ascites or anasarca. A few instances of transitory pedal edema were noted, but these have always been associated with rapidly gathering accumulations in intra-abdominal fat. Studies of anabolic activity, electrolyte and protein metabolism and endocrine system readjustment deserve attention but there has been no clinical evidence of any abnormality of water metabolism.

Therapeutic Effect of Isonicotinic Acid Hydrazine Compounds on the Pulmonary Lesion

As noted, we selected for this study cases of pulmonary tuberculosis which illustrated a variety of lesions ranging from protracted, fibrotic disease with bilateral cavitations to acute, rapidly progressive, exudative, caseous-pneumonic consolidations. We have had opportunity, therefore, to observe the *range* of effect of this new group of compounds in pulmonary tuberculosis. These observations indicate that the therapeutic effect is present not only on the systemic process but also on the infectious element in the local pathological lesion.

Effect on Cough and Expectoration: In every patient treated with isonicotinic acid hydrazide or the derivatives utilized in this study, cough has either been improved or eliminated and expectoration either considerably decreased or eliminated. This has occurred with each drug and at each dosage level although the effects appear to be more remarkable in the higher dosage ranges. This relief from cough and expectoration is rapid. Occasionally, it occurs with dramatic suddeness and on the second or third day of therapy the patient volunteers that his sleep is no longer interrupted by bouts of coughing and his sputum is no longer of its original character and quantity. In other cases, especially with lower dosage ranges, this effect is not noted until the end of the first week or well into the second week of therapy. In all cases, however, except in one in which empyema fluid was being coughed up through a patent broncho-pleural fistula, this effect of therapy was well established by the end of the second week. In most instances, the quantity of the expectoration diminishes before the reduction in frequency of cough. This diminution is most noteworthy. In many instances, shortly after institution of therapy, the paucity of expectoration precludes bacteriological

examination. This effect on cough and expectoration has coincided with the elimination of anti-tussive drugs on our wards. All patients have been allowed free access to anti-tussives upon request but there has been no demand. Codeine was utilized briefly by one patient to alleviate the discomfort of an empyema. Otherwise, it is no longer supplied to our wards.

Diminished expectoration is matched by an alteration in the frequently muco-purulent character of the pre-therapy sputum. The change toward fluidity is usually well established by the second week and at this time the residual cough becomes easier. A single exception to this was noted in one instance wherein the reduction from 40 ounces to four was unaccompanied by loss of purulency. This patient showed evidence of bronchiectasis under an old thoracoplasty and the residual expectoration was deemed to be the product of this disease. Sputum conversion and closure of a large contralateral cavity accompanied the reduction in expectoration.

The decrease in cough and expectoration has been all the more unusual since it has not necessarily correlated with roentgenographic disappearance of cavitation. We must assume sufficient local change in the cavitary lesions so as to reduce or eliminate cavitary secretions. An instance of this decrease in cough and expectoration with residual open cavities follows.

Case Report No. 3: P.R., No. 33311. This 32 year old Puerto Rican female was admitted to Sea View Hospital on June 1, 1949. She had been ill since 1947 and from 1947 to 1949 had been treated with left pneumothorax. From October 11, 1951 to just before onset of therapy with Marsilid on November 23, 1951, she was given a 42 Gm. course of streptomycin for the first time with no effect on either her pulmonary disease or constitutional status. Before institution of therapy with Marsilid, her condition was poor, with temperatures in the subfebrile range. She weighed 93 pounds, a decline of 42 pounds from her normal weight of 135. She was weak and there was a suspicion of broncho-pleural fistula. Review of serial roentgenograms showed continuous progression of a large cavitary disease in the right lung. Under the previous six weeks of streptomycin therapy there was weight loss from 95 to 93 pounds. She suffered from a moderately severe cough, productive of approximately 6 to 8 ounces of muco-purulent expectoration a day. Her sputum was persistently positive on unconcentrated smear, from Gaffky V. to Gaffky X. Figure 5a is a reproduction of a film on September 14, 1951 illustrating the roentgenological status at the onset of therapy.

On November 23, 1951 she began Marsilid at a level of 4 mg./K. Within 10 days her cough was markedly reduced and the quantity of expectoration reduced to approximately 2 ounces a day. In another 10 days her expectoration had almost completely disappeared. Concommitant with the remarkable effect on her cough and expectoration was her rapid clinical improvement. Her appetite improved after one week and has continued to be excellent since. She no longer shows signs of toxicity,

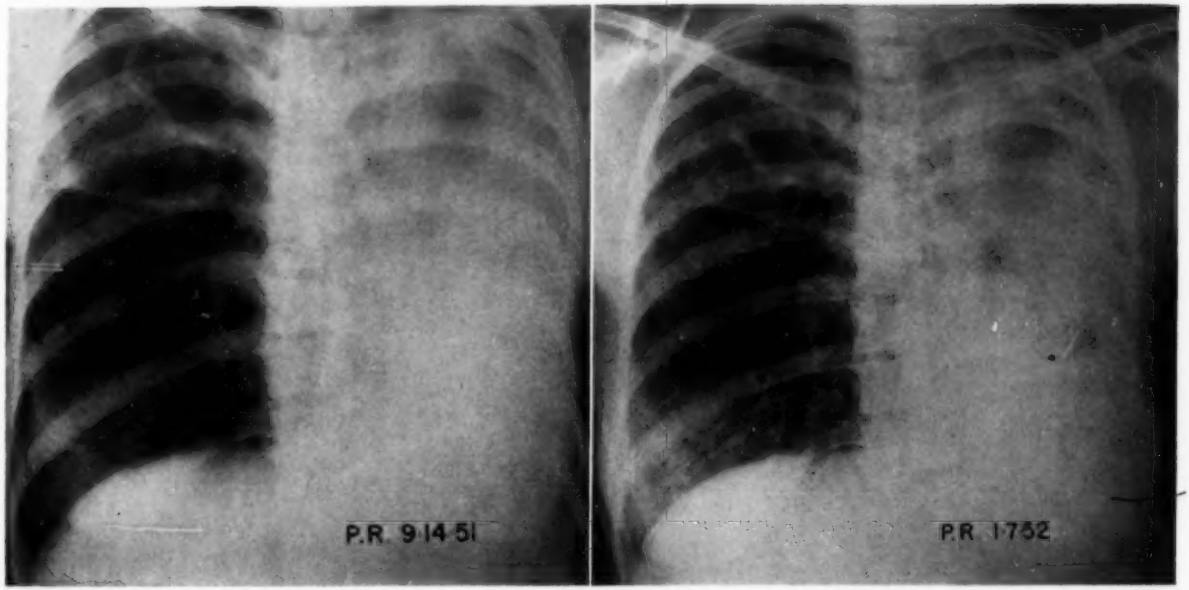

FIGURE 5a FIGURE 5c

FIGURE 5a, CASE P.R.: X-ray film on September 14, 1951, illustrating status at onset of therapy.—FIGURE 5c, CASE P.R.: X-ray film of January 7, 1952. Cavity is still visible, although cough and expectoration are no longer present.

her energy is abundant and her weight loss curve was rapidly reversed. On January 21, after two months of therapy, her weight was 122 pounds, a gain of 28 pounds (Figure 5b). Sputum was positive on four occasions after the onset of therapy including tubercle bacilli found on unconcentrated smear on December 30, 1951. However, smears examined on January 6, 1952 and January 13, 1952 did not contain tubercle bacilli and a concentrate of the gastric contents also failed to show acid-fast bacilli. She continues under treatment. Of interest is the fact that this presently negative sputum and absence of cough has occurred with the persistence of cavitary disease (Fig. 5c). This may be either a local effect on the cavitary economy or may presage cavitary closure. Further observation is continuing.

Bacteriological Examination of Sputum: Elimination of tubercle bacilli from the sputa of patients with pulmonary tuberculosis has long been considered one of the basic essentials for successful tuberculosis therapy. Yet at the inception of this study deliberate de-emphasis of this feature was deemed wise because of the entirely tentative manner in which the dosage schedules were constructed. The ranges utilized were known to be considerably below those determined by the animal studies[3a] to be bacteriocidal. Secondly, cases were selected for study in which the disease was extensive and anatomical restitution hardly to be anticipated. Nevertheless, almost as a corollary to our planned therapeutic observations, our findings, admittedly tentative and limited, have been most encouraging with regard to the effect of therapy with this new group of compounds on the bacteriological contents of the sputum.

Every case, before the onset of therapy had positive sputum.

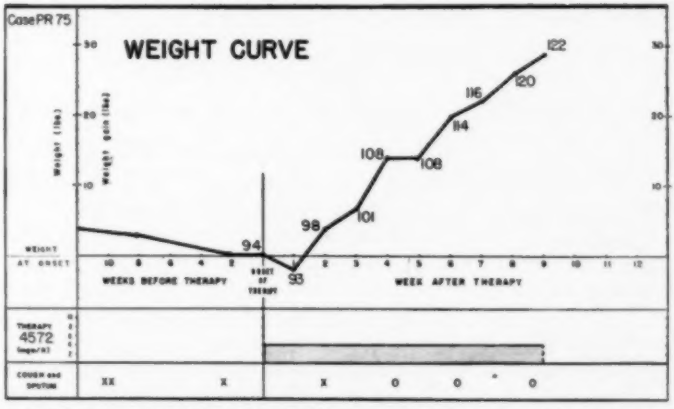

FIGURE 5b, CASE P.R.: Graph illustrating weight gain of 28 pounds in nine weeks of therapy.

In most the sputum was positive on unconcentrated smear, usually in the high Gaffky range (Table VIII).

With from 4 to 15 weeks of therapy, 25 per cent of patients now have sputa which, on examination of concentrated smear and gastric, do not contain tubercle bacilli. Another 28 per cent show occasional positive sputa with a majority of sputum examinations negative on concentrated smear. These patients, of course, are considered as having positive sputum. The remainder of the patients continue to show positive sputum on unconcentrated smear although almost all are now in the lower Gaffky range (Table X).

This brief summary hardly serves as a skeleton for the body of our observations. The significant number of presently negative sputa is as yet unverified by culture due to the brief duration of therapy. Nevertheless, in this group of cases no other means of treatment utilized by us so far has given equal results. Secondly, we feel it equally important to comment on the simultaneous decrease in the total quantity of sputum produced by these and our other patients. Thus, the total number of bacilli expectorated even by those patients who have remained positive on plain unconcentrated smear is greatly reduced; there is significant difference between daily expectoration of 20 ounces of Gaffky X sputum with bacilli crowding every microscopic field, and the production of a bare ½ ounce of Gaffky I sputum in which the bacteriologist must search the entire slide before a single acid-fast rod is found. This difference has pathological implications and is of tremendous prognostic import for the patient although our tabulations continue to carry him as positive.

Many of the patients who are presently negative in the study became negative shortly after the institution of therapy, often

TABLE X

Bacteriological Examination of Sputum After 4 to 15 Weeks of Therapy*

Sputum Range Before Therapy	SPUTUM RANGE AFTER THERAPY — High	Low	Alternating	Negative
HIGH (Gaffky V - X) 53 cases	11	25	12	5
LOW (Gaffky I - V) 34 cases	0	7	13	14
ALTERNATING 5 cases	0	0	1	4
TOTAL	11	32	26	23

*Examination by concentrated smear of sputum and gastric contents.

within the second or third week. The ultimate percentage of conversions is entirely uncertain since many in our compilations, listed as positive at this time, have recently had negative sputa. Their fate is undetermined. An example of sputum negativity occurring in the course of chemotherapy, but with possible residual cavitation, is illustrated by the following case report.

Case Report No. 4: E.S., No. 36599. This 44 year old Negro female was admitted to Sea View Hospital August 14, 1951, three months after the onset of symptoms of tuberculosis. From September to October 1951 she was treated with a 60 gram course of streptomycin following an unsuccessful attempt at right pneumothorax. Para-aminosalicylic acid was simultaneously given. This therapy failed to control her disease and at the time of introduction into this therapeutic series she complained of anorexia, weakness, and a moderate cough, productive of Gaffky IV. sputum on unconcentrated smear. The temperature ranged from 99 to 100 degrees F. during the five months prior to therapy and her weight was stationary at 107 pounds. Her normal weight was 165 pounds. Roentgenograms showed progressive far-advanced caseous-pneumonic tuberculosis (Fig. 6a). She began Marsilid therapy on November 15, 1951, utilizing the 4 mg./K. dosage range. Disappearance of cough and expectoration occurred within a week and there was rapid relief from toxicity and anorexia. In the two months since onset of therapy, she has gained 53 pounds, her weight being 160 pounds on January 21, 1952 (Fig. 6b). Roentgenogram (Fig. 6c) shows marked decrease in size of the right upper lobe cavity and considerable absorption of the exudative disease. The sputum converted to negative in the second week of therapy and has been negative since then on eight consecutive examinations of unconcentrated smears. Gastric examination on January 13, 1952 failed to reveal acid-fast bacilli. She is clinically well, asymptomatic and continues on therapy.

Roentgen Changes

X-ray films were taken at time of institution of therapy and each month thereafter with additional studies performed as indicated. Since therapy was begun at various times between October 2 and December 17, 1951, the x-ray follow-up is variable, ranging from three months in the earlier cases to less than one month in the last group.

No reference to x-ray changes has validity without consideration for the classification of the disease under consideration. For a closer evaluation of the 69 far-advanced and 23 moderately advanced cases herein reported, a modification of the classification of Ornstein et al.[7] has been utilized. Table IX enumerates the numbers appearing in each classification.

An additional sub-classification is appended to indicate by group whether disease was regressive, stationary, progressive or had spread recently before institution of therapy.

The following analysis is tentative since the duration of obser-

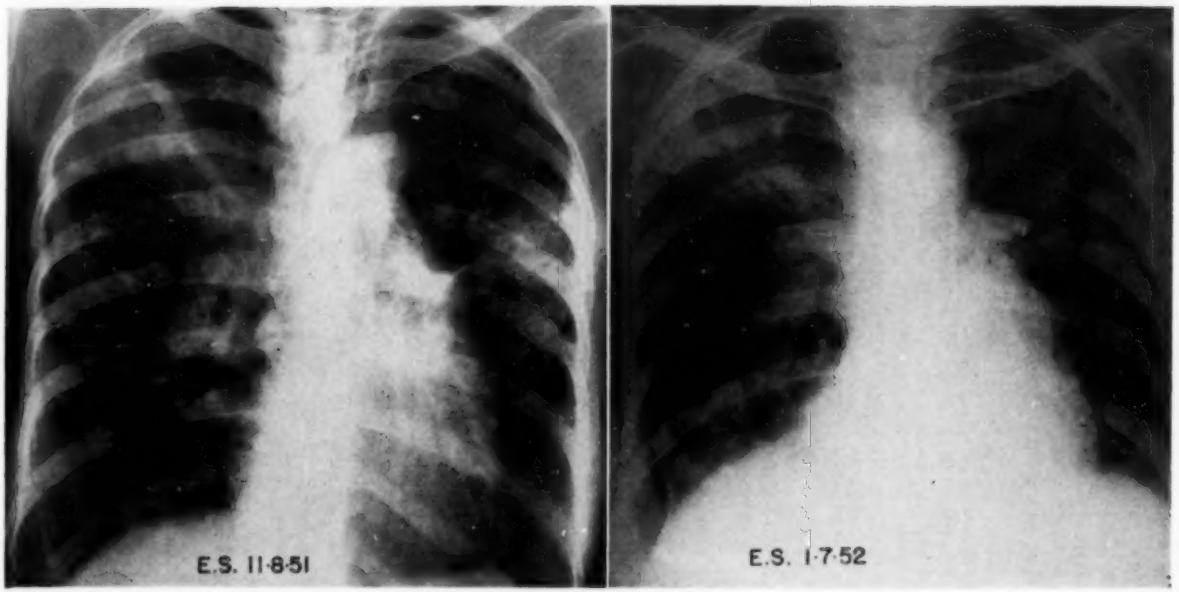

FIGURE 6a FIGURE 6c

FIGURE 6a, CASE E.S.: X-ray film on November 8, 1951 showing bilateral caseous-pneumonic disease. Sputum positive on unconcentrated smear.—FIGURE 6c, CASE E.S.: Roentgenogram of January 7, 1952 showing marked disease in cavity and considerable reabsorption of exudate. Sputum negative since second week of therapy.

vation is obviously inadequate for ultimate definition. The interest centers mainly about the fate of the cavity and of the exudate. Just as sputum in the high Gaffky ranges which enters the "alternating" range is still considered positive, so a cavity which has not completely closed is still considered to be an open cavity. Nevertheless, in a preliminary statement it seems advisable to tabulate reduction in cavity size when it appears to be of significant extent since ultimate complete closure is usually preceded by such diminutions. Table XI summarizes the findings.

We do not feel that those roentgenographic changes noted to date are of crucial significance in the evaluation of the observations above. The anatomical lesions in many, or indeed, most of these cases are largely "irreversible" so that rapid changes are unexpected. Even exudative lesions require sufficient time for resolution. Of great interest, therefore, has been our observation of three cases in which there has been simultaneous diminution in size of three or more cavities within the same lung. Spontaneous closure of an isolated cavity has been repeatedly observed but simultaneous diminution of several is unusual. One of the three has achieved sputum negativity, the other two have exhibited marked diminution in the sputum bacillary counts. Each of the three has experienced dramatic clinical improvement with loss of toxicity, cough and expectoration and return to normal weight. In Table XI, the most rigidly pessimistic criteria have been applied, especially with regard to new exudative disease or cavity formation. In doubtful instances, with variations in roentgenographic tech-

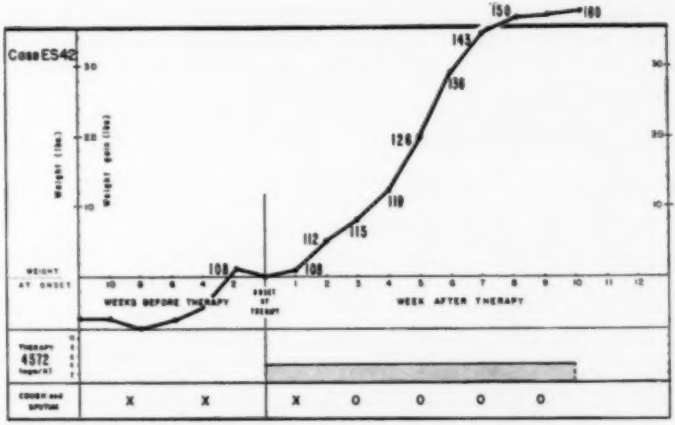

FIGURE 6b, CASE E.S.: Weight graph of case E.S. showing gain of 53 pounds in 10 weeks of therapy.

TABLE XI: X-ray Changes — 92 Patients

GROUPS	No Significant Change	Clearing Exudate	Cavity Appreciably Smaller	Cavity Closed	Cavity Smaller and Clearing Exudate	Extension of Exudate	New Cavities	Cavity Larger	Total
Group I — Marsilid 2 mgs./K. from 10/2/51 4 mgs./K. from 11/20/51 15 patients	5	1	4		2	2	1		15
Group II — Marsilid 2 mgs./K. from 10/15/51 4 mgs./K. from 11/20/51 6 patients		2	1	2	1				6
Group III — Marsilid 2 mgs./K. from 10/25/51 4 mgs./K. from 11/20/51 7 patients	2		3		2				7
Group IV — Marsilid 4 mgs./K. from 11/15/51 28 patients	13	4	9						28
Group V — Marsilid 4 mgs./K. from 11/23/51 16 patients	5	3	5		2	1			16
Group VI — Marsilid 10 mgs./K. from 12/6/51 10 patients	5		4			1			10
Group VII — Rimifon 2 mgs./K. from 12/17/51 4 mgs./K. from 12/24/51 10 patients	10								10
TOTALS	42	10	26	2	7	4	1	0	92

nique, the exudate was considered to have increased. In one case, a highlight was noted within a previous area of exudate and was considered a cavity. Tomographic x-rays are being performed for confirmation.

Correlation of the sputum findings with the x-ray shadows has been of unusual interest in view of the frequency with which negative sputum and gastric examinations have been noted among patients whose cavities have remained patent. We occasionally observe this with streptomycin and thiosemicarbazone. It has often been seen in this series and of the 23 patients with negative sputum, review of recent roentgenograms still shows patent cavities in 14 and probably, although not definitely, cavitation in seven. This apparent contradiction has been especially frequent among patients whose cavities are diminishing in size and since it is a frequent observation that cavities which ultimately close appear to predict this by previous negativity of sputum, it may well be that our subsequent interval report will include these within the "cavities closed" column. An attempt has been made to correlate the x-ray findings with the sputum findings and this is recorded in Table XII. It should be noted that patients with sputa still positive and cavities still open have had considerable clearing of exudate. The significance of these is uncertain in view of the natural tendency for exudate to resolve.

Extrapulmonary Tuberculosis

Any series of 92 patients with well-established pulmonary tuberculosis will concommitantly display extra-pulmonary tuberculosis and tuberculosis of the excretory passages. Our group is no exception. Observations have also been made in patients with extra-pulmonary tuberculosis without lung lesions and will be the basis of reports dealing with the special problems which they represent.

The most commonly encountered extra-pulmonary lesion in our series was tuberculous laryngitis. This occurred 10 times. No effort

TABLE XII

Relation of Cavity to Sputum

	Open Cavity Number of Patients	Closing or Smaller Cavity Number of Patients	Cavity Closed Number of Patients	Totals Number of Patients
Positive Sputum	25	18		43
Alternating	18	8		26
Negative	14	7	2	23
TOTAL	57	33	2	92

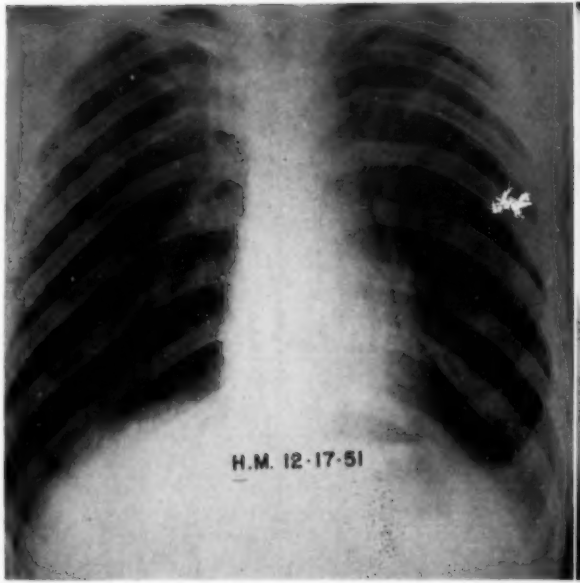

FIGURE 7a

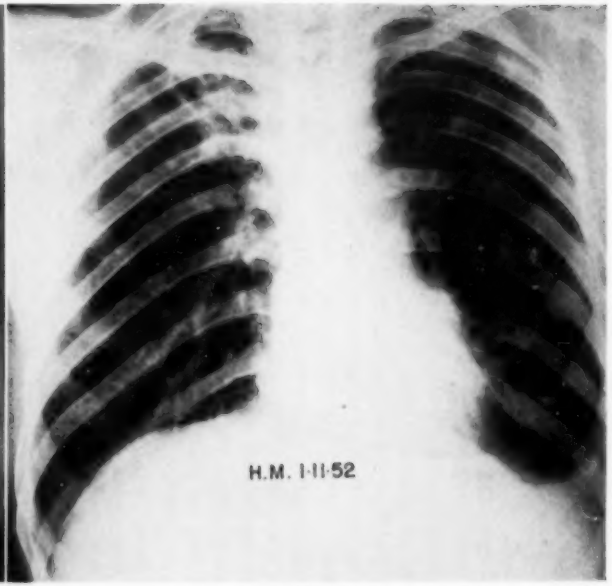

FIGURE 7c

FIGURE 7a, CASE H.M.: X-ray film of December 17, 1951 showing bilateral upper lobe cavitation at onset of therapy.—FIGURE 7c, CASE H.M.: X-ray film of January 11, 1951 shows diminution in cavity size and reabsorption of exudate. However, despite negative sputum, cavity is still open.

is made in this report to describe the laryngoscopic findings since these are being studied by our Otolaryngology Service. However, it is well within the field of clinical observation to note the changes in voice clarity and to accept the testimony of patients on deglutition. Utilizing the latter criteria, success was obtained in every instance. All patients had had one or more courses of streptomycin, deemed to be adequate for the control of this condition. None had received permanent therapeutic benefit therefrom. The beneficial results were rapidly apparent in all instances and appeared to match the time schedule usually noted with streptomycin therapy when that drug is effectual. The most salutory results were those noted at the 10 mg./K. level of Marsilid. Therapy with Rimifon is also effectual. Clinical relapse has not yet been seen. The following case report is illustrative.

Case Report No. 5: H.M., No. 34471. This 27 year old Puerto Rican male was admitted to Sea View Hospital on October 24, 1951. Symptoms of his pulmonary tuberculosis had their onset in 1948 and in 1949, 1950 and 1951 he had had three courses of streptomycin and para-aminosalicylic acid totaling 126 grams of streptomycin. He had a total of eight months of para-aminosalicylic acid. Pneumothorax therapy in 1951 was abandoned after two internal pneumonolyses failed to improve the collapse. A pneumoperitoneum in 1951 had been similarly abandoned as ineffectual. He began to show symptoms of tuberculous laryngitis in 1949 and this continued for the next two years showing no improvement during the courses of streptomycin. Roentgenogram (Fig. 7a) showed bilateral upper lobe cavitation. Immediately before onset of therapy with Marsilid, his tuberculous laryngitis was moderately severe. He was hoarse and was unable to take citrus fruit juice or hot food without pain. A moderate cough was productive of 8 ounces of sputum daily and in the

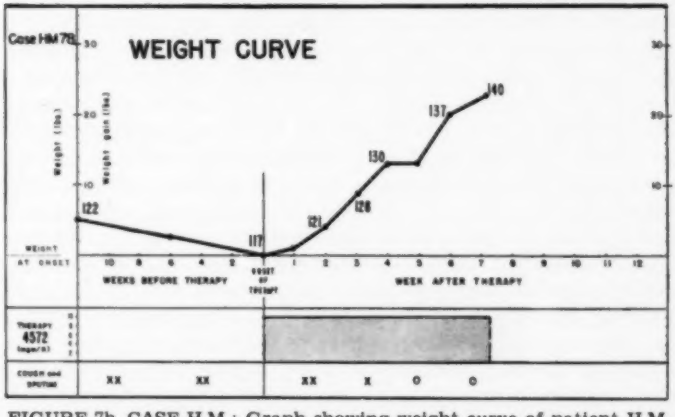

FIGURE 7b, CASE H.M.: Graph showing weight curve of patient H.M. Slow weight loss ceased with institution of therapy and in seven weeks there has been 23 pounds of weight gained.

previous three months he had lost five pounds so that at the onset of therapy he weighed 117 pounds. His temperature approximated 99 degrees F.; he had moderate anorexia.

On December 5, 1951 he started Marsilid therapy, at a level of 10 mg./K. Two days later he no longer had laryngeal pain and within several days after that the hoarseness began to clear. With this, clinical improvement was rapid. Within three weeks of therapy, cough and expectoration had ceased and the progressive weight loss had been halted. At the present time, he has gained 23 pounds and in seven weeks of treatment has been liberated of all laryngeal symptoms. His appetite is excellent. His sputum, positive for tubercle bacilli before therapy (Gaffky IX on plain unconcentrated smear) was negative on the 10th day of therapy and has continued so on five examinations since, including gastric examination on January 13, 1952. His roentgenogram has shown definite decrease in the size of his cavity in the right upper lobe, but this is still present despite the negative sputum. The patient continues with therapy.

Tuberculous otitis media has also been treated successfully. This, too, will be the subject of a later report. Tuberculous enteritis, a disease which has been shown to exist in almost all patients with progressive caseous-pneumonic disease who exhibit temperature elevation for two or more months,[11] was presumably present in almost half of the patients treated. Symptomatology, where present, cleared promptly and has not recurred. Further studies in this regard are being planned. The short term results in bone and joint tuberculosis have also been the subject of study and are reported by the director of the Orthopeodic Service, Dr. David Bosworth.[14] Suffice it to state that Marsilid exerts a beneficial effect in these cases. Severe tuberculosis of the tongue has also been under therapy and this patient is included in the series reported here. He had received intensive streptomycin therapy at another institution before admission to Sea View. No benefit had been obtained and the course was one of progression of ulceration. The effects in this instance were so rapid and profound that a detailed report is currently in preparation. Instances of tuberculous meningitis deemed to have failed with streptomycin therapy are also under observation and the preliminary estimates suggest a possibly favorable outcome. A series of children with tuberculous disease are under therapeutic investigation in the Pediatric Division and will be reported at a later date by the director of pediatrics, Dr. Bret Ratner. Studies are being conducted in relation to the pre-operative care of the thoracic surgical patient. Intensive investigations are also under way in the management of the thoracic surgical failure. The effect of isonicotinic acid hydrazide therapy in silico-tuberculosis is under investigation and in this regard particular attention will be directed toward the studies of pulmonary function. Combined therapy utilizing adjunctive streptomycin has been begun. A study of the effects of the isonicotinic

acid hydrazides on genito-urinary disease, and other investigations into the many varieties of tuberculous lesions which are encountered in the huge patient population of Sea View Hospital, are being conducted and will be the subject of later reports.

Toxicological Observations

Toxicological studies on the three drugs utilized in our investigation have been both clinical and laboratory. At the beginning of our study, examinations were made frequently as noted above. At the present time we continue to do complete blood counts, urine examinations, sedimentation rates, cephalin flocculation tests and serum protein studies approximately every three weeks. Electrocardiograph examinations have been done on half the patients. Clinical examination is made daily. Special examinations such as vestibular function tests, liver function tests and kidney function tests, have been done where indicated.

Administration of 1-isonicotinyl-2-glucosyl hydrazine covered a nine week split period from June to October 1951. This drug was given subcutaneously in combination with isonicotinic acid hydrazide.[5] Isonicotinic acid hydrazide (Rimifon), was again given later, as reported in this paper, in oral tablets. The 1-isonicotinyl-2-isopropyl hydrazine (Marsilid) was also given orally. Comments with regard to our findings on the human toxicology of these substances will apply to all three, except where differences among them exist, in which case these differences will be noted.

Local Effects: Local effects were noted with subcutaneous administration of the glucosyl derivative. These consisted principally of transitory pain and swelling at the site of injection. It occurred after five to six weeks of therapy and were possibly due to the greater proportion of the isonicotinic acid hydrazide present in the material. With oral administration of Marsilid and Rimifon there has been no evidence of local irritating effects, neither of the mouth nor the remainder of the gastro-intestinal tract.

Skin Rash: No skin lesions that can be stated with certainty to be due to therapy have been noted, apart from the subcutaneous swelling described above. One patient exhibited urticaria, but this was found to be due to sensitivity to ingestion of cheese. It has not recurred with the removal of cheese from her diet. Another patient, after several weeks of therapy, developed a generalized rash. Consultation with our Dermatology Service elicited the opinion that this was due to generalization of a fungus dermatitis. The patient had generalized exfoliation but recovered completely in four weeks. After a new test dose, he was restarted on therapy and has continued for one month without recurrence of his skin

TABLE XIII: Toxicity Table

Group I: 28 Patients; 2 mgs./K.; 4 to 7 Weeks (Marsilid) and at 4 mgs./K. for 9 Additional Weeks

		— — — 2 mgs./K.: October 2, 1951 to November 20, 1951 — — —									
		— — Weeks at Which Symptoms Were Noted — —									
SYMPTOMS	Number of Patients	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	Number Times Noted
Vertigo	9	4	2	4	1			2			13
Constipation	8	5	3	2				1			11
Twitching of Lower Extremities	4		1	1	2	1	1	1			7
Drowsiness											
Insomnia	1	1									1
Headache	1							1			1
Weakness of Legs	1						1	1			2
Disturbed Vision	1				4						4
Hyper-Reflexia	3		2	1	2	1	1	1			8
Delay-of-Starting-Stream											
Tinnitus											
Dryness of Mouth											
Skin Rash	1	1									1
Exertional Dyspnoea	2	1	1	1	1			1			5

TABLE XIII: Toxicity Table (Continued)

		— — — 4 mgs./K.: November 20, 1951 to January 15, 1952 — — —									
		— — Weeks at Which Symptoms Were Noted — —									
SYMPTOMS	Number of Patients	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	Number Times Noted
Vertigo	13	7	4	5	8	2	2	1	4	1	34
Constipation	6	1	2	3	4	3					13
Twitching of Lower Extremities	22	5	8	8	9	13	6	9	6	3	67
Drowsiness	6	1		1	1	3		1	2	1	10
Insomnia	7	1		1	3	3			2	1	11
Headache	2	1			2	2					5
Weakness of Legs	9	1	3	5	5	3		2	1	1	21
Disturbed Vision	2	1	1			1					3
Hyper-Reflexia	14	4	3	4	8	7	1	3	4	3	37
Delay-of-Starting-Stream	7	1	1	1	3	4	4	2	1		17
Tinnitus	3		1	3	2	2	2	1			11
Dryness of Mouth	2	1	1	1							3
Skin Rash											
Exertional Dyspnoea	3	1		1	1	1	1	2	1		8

TABLE XIV: Toxicity Table

Group II: 44 Patients; 4 mgs./K.; 9 weeks (Marsilid)

		— — 4 mgs./K.: { November 15, 1951 / November 23, 1951 } to January 15, 1952 — —									
		— — Weeks at Which Symptoms Were Noted — —									
SYMPTOMS	Number of Patients	1	2	3	4	5	6	7	8	9	Number Times Noted
Vertigo	33	17	8	15	17	8	9	9	3	6	92
Constipation	29	10	8	13	14	6	8	11	2	5	77
Twitching of Lower Extremities	33	4	3	17	21	11	19	17	7	12	111
Insomnia	14	3	2	5	2	1	2	3	1	4	23
Drowsiness	18	4	4	8	5	3	4	7	4	6	45
Headache	12	1	1	6	6		1		1	1	17
Weakness of Legs	25	4	6	14	14	13	15	6	6	7	85
Disturbed Vision	8	2		3	3		1	2			11
Tinnitus	4	1	2	1	1			1			6
Hyper-Reflexia	29	2	2	15	17	9	11	5	1	5	67
Delay-of-Starting-Stream	25	2	11	19	18	7	8	10	4	5	84
Dryness of Mouth	13		2	5	3	1	4	3		2	20
Exertional Dyspnoea	6		1	1	3	2	2	2	1		12
Polyuria	2			1		1	1	1			4
Skin Rash	4		1	1	3	2	1				8

TABLE XV: Toxicity Table

Group III: 10 Patients; 10 mgs./K.; 7 Weeks (Marsilid)

SYMPTOMS	Number of Patients	10 mgs./K.: December 5, 1951 to January 15, 1952 — Weeks at Which Symptoms Were Noted									Number Times Noted
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	
Vertigo	8	6	4	4	5	3	1				23
Constipation	7	2	5	4	3	2	1				17
Twitching of Lower Extremities	10	1	3	5	5	4					16
Insomnia	4		2	1	2	1					6
Drowsiness	3		1	1	1	1	1				5
Headache	3		1	2							3
Weakness of Legs	9		2	3	3	4	2				14
Disturbed Vision	2	1			2						3
Tinnitus	3	1	2	3							6
Hyper-Reflexia	9		3	4	5						12
Delay-of-Starting-Stream	6			5	3	1					9
Dryness of Mouth	5		1	3	1						5
Exertional Dyspnea	3			2	1						3
Polyuria	1			1							1

TABLE XVI: Toxicity Table

Group IV: 10 Patients; 2 mgs./K.; 1 Week and 4 mgs./K.
3 Additional Weeks (Rimifon)

SYMPTOMS	Number of Patients	— — *Weeks at Which Symptoms Were Noted* — —									Number Times Noted
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	
Vertigo	1			1							1
Constipation	2		2		1						3
Twitching of Lower Extremities	3		3								3
Drowsiness	1	1									1
Headache	2	1		1							2
Hyper-Reflexia	1		1								1
Delay-of-Starting-Stream	1		1								1
Dryness of Mouth	1		1								1

lesion. Skin lesions are being watched for with continuance of therapy.

Allergic Reactions: There has been no evidence of antigenicity to date. We treated a group of five patients with a seven week course of the isonicotinic acid hydrazide and its glucosyl derivative in June and July 1951. This has been reported elsewhere.[5] These patients were then given no medication for a seven week period. Restarted on the same therapy, no evidence of allergic reaction was seen. We have had no clinical evidence of allergic reaction to any of the drugs given orally (Marsilid and Rimifon). However, we have noted a moderate eosinophilia in a number of instances. On one occasion a patient showed an eosinophilia of 20 per cent while others have exhibited eosinophilia ranging from 6 to 16 per cent. These, however, are not constant, vary from patient to patient and are variable for each patient. They are not frequent. They are unassociated with clinical evidence of allergy and they have no such correlation. As is known, eosinophilia does occur coincident with the healing process in tuberculosis.

Hyper-reflexia: This is probably the most frequent symptom noted, as seen by the analysis of Tables XIII, XIV, XV, and XVI. This was found on examination of deep reflexes but may be suspected from patient's statements of "leg twitching" occurring principally at night but also during the day. This tends to appear early in therapy, usually by the first or second week and is somewhat more frequent at the higher dosage range. Clinically it is a minor symptom. It has more pharmacological than clinical interest.

Vertigo: This symptom has been next in frequency to hyperreflexia. Usually it appears in the first or second week, especially at the higher dosage ranges. It has apparently been more common with Marsilid than with Rimifon. It has occurred with greater frequency and to a more clinically significant degree in patients of the older age groups than in the younger patients. Usually, it is merely annoying, but occasionally it has been troublesome, especially in older people. It is often complained of upon rising in the morning but can appear at any time. It is aggravated by rapid changes of position, but occasionally occurs even without it. Our studies indicate that it is possibly vasomotor in origin. It is not associated with elevation in blood pressure, or notable changes in pulse rate. It is aggravated by adrenergic drugs such as ephedrine. It is most frequently seen at the fourth or fifth week of therapy and then tends to disappear. However, it may also be present in later weeks of therapy. Its incidence and correlations are noted in Tables XIII-XVI.

Constipation: This symptom is occasionally troublesome. It occurs in a fair number of patients and is seen again early in the

course of therapy. We believe it an autonomic nervous system effect. When this is present, the patients often feel ill and we have seen elevations in temperature coincident with it, alleviated by relief of constipation. Cathartics and enemata are utilized where necessary. Constipation fails to be a troublesome symptom after the first four or five weeks of therapy. We have the impression that it is somewhat more frequent with Marsilid than with Rimifon, although correlations with corresponding therapeutic dosage ranges will be necessary here before definitive opinion be given.

Urinary Bladder Retention: This symptom appeared in several patients and consisted of inability to initiate urinary flow. Catheterization was necessary. It occurred in females as well as males. However, it was not a troublesome symptom as it disappeared promptly. It was infrequent after the fourth or fifth weeks of therapy.

Alterations of Mood: With higher dosage ranges, especially of Marsilid, there is a subtle general stimulation to be noted. This was not particularly noticeable with patients at the 2 and 4 mg. levels, nor even the 10 mg. level. However, it was noted occasionally in all three dosage ranges and was noted in as yet unreported studies with higher dosage levels. Drowsiness, on the other hand, was occasionally commented upon by patients, but was intermittant and evanescent. However, here too, with doses above 10 mg./K. of the isopropyl derivative it was more clinically significant.

Variations in Sexual Activity: Variable findings have been noted in this regard. With clinical improvement and return of vigor, increased sexual activity was commented upon. On the other hand, in those patients clinically well, diminution in sexual desire was sometimes volunteered. Data are inadequate for statistical analysis. In addition, variations in the physiological status of sexual activity have also occasionally been volunteered. These variations were present at all dosage levels.

Other Symptoms: Occasionally patients complained of evanescent disturbance of vision, particularly in the morning. It is difficult to explain this, since blood level studies so far available would indicate that there is little or no drug detectable in the blood stream at this time. Some patients also commented upon dryness of the mouth, but this was not troublesome. Occasionally, headache was noticed, quite severe on one or two occasions. It was aggravated by ephedrine. Occasionally, patients stated that their sleep was sometimes interrupted by restlessness; other patients stated the reverse. Tinnitus was infrequently noted, and was of brief duration.

Laboratory Studies: Findings in this regard have principally

been negative to date. All cephalin flocculation tests have been normal as have other biochemical studies. Hematological findings, which will be reported in more detail elsewhere, show a minimal drop in hemoglobin levels after several weeks of treatment with spontaneous restitution without therapy. There have been no changes in the white cell series apart from the eosinophilia noted above. Electrocardiograms in approximately 40 of the patients have shown no variation from normal. Urinary findings in almost all patients have been remarkable for their absence of deviation from normal. However, proteinuria was seen in two patients. In one, proteinuria was present in large amounts prior to the onset of therapy, due to probable amyloidosis (there was 95 per cent congo red absorption[12]) and this proteinuria continued unchanged after the onset of therapy. It was of interest in this patient, with evidence of a nephrotic syndrome, to note that non-protein nitrogen was 46 mg. per cent before onset of therapy and went down to 36 mg. per cent after seven weeks of therapy. A second patient showed occasional small amounts of protein in the urine before the onset of therapy, coincident with an acute gastroenteritis. Renal function studies are being performed. Apart from these findings, there has been an occasional trace of protein and an occasional cast among the many urines examined. On one or two occasions reducing substance was found in the urine but was absent in subsequent examinations. Preliminary histological studies were also available on the parenchymatous organs of the two patients (J.A. and S.W.) who died while under treatment (see above). Autopsies were performed on both patients and nothing of note was found in liver, spleen, kidney or bone marrow.[13]

The above toxicological findings are tentative and incomplete. Obviously, they represent only observations of "acute" toxicity. Duration of therapy, especially at the higher dosage ranges, is much too short for adequate evaluation of clinical toxicity. This is especially true with regard to isonicotinic acid hydrazide (Rimifon). With this drug, animal studies[4a] would indicate that long continued administration is perhaps more likely to result in toxic parenchymatous damage than with Marsilid. Long term toxicity studies are therefore of considerable importance and findings in these studies will undoubtedly influence decisions with regard to dosage levels, duration of therapy, etc.

Similarly, studies so far conducted give no valid answer with regard to variations of acute toxicity between Marsilid and Rimifon. Our impression is that mg. for mg. Rimifon shows fewer side effects and that those which do occur are of less degree. However, this may have no correlation with organ toxicity, especially with continued administration. Also, toxicity may prove to be quite

comparable when adequate therapeutic dosage levels are correlated.

Review of the tables in this section indicate that as the dosage levels increase beyond minimal range, side effects tend to increase both in number and severity. However, they qualitatively occur at all levels. Also, beyond 4 mg./K. of Marsilid there seems to be no significant increase in side effects until high dosage levels are reached. Data with regard to Rimifon are as yet inadequate in this regard although, here too, increase in dosage from low ranges to the high ranges has been associated with increase in side effects.

Many of the side effects appear to be vasomotor in origin, probably indirectly through sympathetic stimulation. This latter was suggested by the constipation, bladder sphincter disturbance and dryness of the mouth. There has been no apparent pressor effect. Symptoms are aggravated by ephedrine, belladonna and possibly by pyribenzamine and in some instances have been ameliorated by prostigmine bromide. It would appear desirable, until further pharmacological studies are made, to refrain whenever possible, from simultaneous administration of other drugs, particularly those with adrenergic activity. Urine findings are being further studied clinically and animal laboratory investigations in this regard are desirable.

Observations in this section are based on experiences of brief duration and studies of limited extent. Further clinical toxicological studies are important and should be pursued. Also evidences of chronic toxicity are still to be sought and evaluated. This is particularly true with regard to Rimifon. Nevertheless, there has been no evidence to date to contraindicate further clinical investigations of this group of compounds, especially in the light of the therapeutic data so far accumulated.

Discussion

Our investigations, outlined above, indicate that the hydrazides of isonicotinic acid are effectual in the treatment of tuberculosis in humans. The mechanism of such chemotherapeutic activity is uncertain and it may be that it is mediated through some as yet obscure variation in allergic, endocrine or metabolic function. Still, accumulating evidence indicates that these compounds are, per se, potent anti-tuberculosis agents.

The data in this preliminary report are of value in assessing the therapeutic activity of the drugs. Yet their thorough analysis fails to capture the flavor of what we have observed on our wards. The abrupt cessation and rapid reversal of the progressive downhill courses of many of the patients in our series cannot be completely conveyed in statistics. Many of these patients, at this writing, are still sputum positive and still have open cavitary

lesions. But our experiences with many thousands of such cases in an institution which for years maintained its census of over 2,000 patients and had a turnover of at least half of these each year, tells us that many of these patients would now be dead. Instead, they have had complete elimination of the toxic effects of tuberculous disease, have gained 20 or 30 or more pounds and are normal in every respect excepting for the presence of acid-fast bacilli in the sputum and ring shadows on the x-ray films. These we presently list as failures in accordance with the strictest criteria.

It is difficult to state which of the effects we have observed have been most dramatic. Possibly the return of appetite and the extraordinary weight gain are the most remarkable. Gains of 50 and 60 pounds are not uncommon and the tendency to level off when the normal weight has been regained indicates the elimination of the depressive toxic effects of this disease, rather than the introduction of some agent operating anabolically for purposes of fat deposition alone. That this weight gain is not the result of abnormal accumulations of fluid became apparent after numerous careful examinations of the patients exhibiting the greatest increases. That it is not the result of depressive action upon the thyroid is also evident from the most cursory observations of patients, who exhibit none of the stigmata of the hypothyroid state. Indeed, if anything, the appearance is one of increased rather than diminished thyroid activity. This effect, we have learned, is probably the result of mild stimulation of the central nervous system. The appetite increase and weight gain go hand in hand. References to our data indicates that the weight gain may be correlated with the dosage of the drug employed.

From the point of view of the clinician, the rapid decline of temperature to normal has special significance. Patients whose temperatures ranged from 103 to 105 degrees F., over many months prior to therapy, experienced precipitous fall in temperature, occasionally within a day, but always by the second week. These drops were always accompanied by reversal of the original toxic states. Return of strength and energy have not been delayed and patients who were bedridden for two or more years became fully ambulatory within a few weeks. All patients on therapy are now ambulatory.

The immediate and continuing diminution or elimination of the toxicity and systemic manifestations of the tuberculous process, may make utilization of this group of compounds of importance chemotherapeutically beyond their own inherent anti-tubercular range. Thus, experience will indicate their possible use as an adjunct to collapse procedures or in the preparation of patients

with extensive destruction of lung tissue for excisional surgery. However, since the therapeutic scope of this new series of compounds is as yet incompletely explored, it may be that their use will obviate the necessity for some of these procedures.

Further, the degree of effectiveness of these drugs on the toxicity of tuberculosis may be gauged by the fact that it was apparent not only in the obviously toxic, febrile patient but also in the chronically ill, long-standing "chronic" disease, wherein the subtle debilitating systemic effects are often ill-defined and clinically undetected. Thus, we found that these patients, too, gain weight and feel better (Cf Case 2, M.N.), cough less, and have increased strength. Metabolic balance studies would be of interest in these cases as well as in those of more dramatic aspect. The effect of the hydrazides of isonicotinic acid will indeed form a fruitful field for metabolic and endocrine research.

Diminution or total elimination of cough and expectoration have also been of striking degree. Many patients who had previously reported expectoration of 32 to 40 ounces of sputum per day, now expectorate minor fractions of their original output. In instances of concommitant bronchiectasis we can almost quantitate the fractions due to tuberculosis and those due to the bronchiectasis. Diminution to a certain level readily occurs and this has been interpreted as the tuberculosis fraction. It has been seen in patients who have been rendered negative on sputum and gastric examination in whom there is good evidence of the presence of bronchiectasis. This is of particular significance since the experimental work to date suggests that the hydrazide derivatives of isonicotinic acid exert no influence over non-acid-fast organisms. Diminution in expectoration is usually preceded by the patient's observation that the sputum has changed its character and color, becoming thin and white, where it was formerly thick and often greenish.

Among the more important additional studies at present under investigation, are those relating to the resistance of acid-fast bacilli to the isonicotinic acid hydrazides. Clinically, we can say that patients under therapy for four months have exhibited no such resistance. With streptomycin therapy we have usually noticed a gradual return of cough, expectoration and elevating sputum bacillary content in patients with massive caseous-pneumonic tuberculosis under prolonged streptomycin therapy. The patients in this series have retained the gains they have achieved despite continuation of therapy. If experience with other antitubercular chemotherapeutic and antibiotic agents indicates a general rule, ultimate resistance may be anticipated. If, on the other hand, this drug is bacteriocidal prompt application of a definitive dose

may avoid this outcome. Detailed investigations on bacterial resistance are being conducted by our Bacteriologist, Dr. Arpad Berczeller. Our own preliminary and fragmentary observations to date on sputum cultures of patients positive after one, two and three months of therapy, have yielded no evidence of resistance of the bacteria in these sputa to the drug utilized for treatment.

Dosage and the proper administration of the drugs was arbitrarily devised in the early phases of this investigation by reference to the available evidence deduced from the animal study. In order to retain the widest possible margin of safety, the first administrations were at the 1 mg./K. level.[5] This was rapidly increased and we have now studied graduated dosage levels of the drugs here reported. It may be stated that all of the drugs and dosages employed have been effectual. Therapeutic effects have been more rapid in the higher dosage ranges, but so indeed, has been the incidence of side reactions. The larger questions relating to blood and tissue levels which have been widely discussed with relationship to streptomycin, para-aminosalycilic acid and the thiosemicarbazones, naturally have application with the agents under discussion. Whether or not the maintenance of therapeutic levels is necessary or desireable remains unanswered, but both clinical and laboratory investigations into this problem are currently being conducted. We do know that the levels we have achieved are effectual. We also know that it is probably possible to maintain continuous high levels through alterations in administration schedules.

The toxic side effects have been described. It is important to differentiate between the so-called acute toxic effects and the chronic toxic effects. The latter relate to parenchymatous organ effects, notably liver and kidney, where degenerative changes are most commonly observed. The acute effects are not nearly so readily observable in animals and preliminary laboratory studies did not forewarn us as to the nature of the phenomena subsequently observed. The effects manifested themselves in a variety of ways but were almost exclusively limited to the autonomic and central nervous systems. Severe constipation, at times almost to the point of paralytic ileus, was a common complaint. Vertigo was another frequent phenomenon and revealed itself as a vasomotor effect since it was accompanied by fall in systolic blood pressure and elevation of the pulse rate. The mechanism has not been entirely clarified in our clinical studies. Interval blood pressure observations indicate a complete absence of pressor effect. Further pharmacological investigations in this regard are desirable. That the central nervous system probably also receives some

stimulation is suggested by the hyper-reflexia of the deep reflexes, by the frequent complaints of leg-twitching, by the occasional reports of insomnia and by some degree of apparent exhilaration among the patients studied.

Other toxic side reactions have been gratifyingly absent. There has been no gastro-intestinal distress other than the constipation noted above. No skin rashes which could be attributed to the drug have been noted. Laboratory examinations so far have similarly revealed little of significance. Equivocal effects on hemoglobin to date suggest absence of definite effect on the hemopoetic system. Urine examinations occasionally revealed traces of albumin but only in one case has the amount been significant. One patient with probable amyloidosis and persistent heavy proteinuria in the pre-therapy period continued to have proteinuria. The salutory effects of therapy in this patient are revealed by diuresis and loss of tissue edema in the second week of therapy, persistent gain in weight and well-being, sputum negativity and closure or apparent closure of a multiple cavitary process in the left lung. The effect of the control of the tuberculous disease on the secondary amyloidosis in this case will be the subject of intensive study.

SUMMARY AND CONCLUSIONS

1) Ninety-two patients with moderately or far-advanced pulmonary tuberculosis classified largely as progressive and caseous-pneumonic, have been treated with the hydrazide of isonicotinic acid (Rimifon) and its isopropyl derivative (Marsilid).

2) All patients had positive sputum and active disease before institution of therapy. Forty-five were toxic and febrile.

3) Patients, divided into groups, were treated with 2, 4, and 10 milligrams per Kilo of Marsilid and 4 mg. of Rimifon for from four to 15 weeks.

4) Complete elimination of fever and toxicity occurred within two to three weeks in all cases. Appetite increase and restored sense of well-being were matched and overshadowed by weight gains which varied up to 64 pounds and averaged 18 pounds at an average of nine weeks of treatment.

5) Sputum negativity was obtained in 25 per cent of patients in from four to 15 weeks of treatment and in another 28 per cent, sharp reductions from consistent plain smear positivity to "occasionally positive" occurred.

6) Cough and expectoration were completely eliminated, or almost so, in from two to three weeks.

7) Among the 92 cases, in from four to 15 weeks, cavity closure

occurred in two cases, marked reduction in cavity size was noted in 33 cases, clearing of exudate occurred 17 times.

8) Marked simultaneous diminution in several cavities within the same lung was seen three times.

9) Extension of exudate occurred four times and was minimal. One equivical new cavity appeared at the site of a pre-therapy exudate.

10) There was no death due to progression of tuberculosis.

11) Cure or marked improvement has been seen in cases of tuberculous laryngitis, tuberculous otitis, tuberculous glossitis.

12) Toxic effects of Marsilid and Rimifon therapy include hyperreflexia, leg-twitching, constipation, vertigo and reflex disturbance of micturition.

13) No death due to therapy has occurred.

14) Every patient has been benefited by therapy.

15) Clinical investigation of these previously untried new compounds, the hydrazide of isonicotinic acid (Rimifon) and its isopropyl derivative (Marsilid) reveals that they are potent agents for the treatment of human tuberculosis.

RESUMEN

1) Noventa y dos pacientes con tuberculosis pulmonar moderada o muy avanzada clasificada con mucho como progresiva y caseo-neumónica han sido tratados con la hidrazida del ácido isonicotínico (Rimifón) y su derivado isopropilo (Marsilida).

2) Todos los pacientes tenían esputo positivo y enfermedad activa antes del comienzo de la terapia. Cuarenta y cuatro tenían manifestaciones de toxicidad y eran febriles.

3) Los pacientes divididos en grupos fueron tratados con 2, 4 y 10 mg. de Marsilida por Kilo y 4 mg. de Rimifón por de 4 a 15 semanas.

4) La completa eliminación de la fiebre y de los fenómenos tóxicos ocurrió en dos a tres semanas en todos los casos. Aumentó el apetito y se recuperó la sensación de bienestar y esto fué acompañado por un aumento de peso que llegó a ser de 64 libras con un promedio de 18 libras a las 9 semanas de tratamiento.

5) Esputos negativos se obtuvieron en un 25 por ciento de los pacientes en de cuatro a quince semanas de tratamiento y en otro 28 por ciento disminución de bacilos hasta ser ocasionalmente positivos.

6) La tos y la expectoración fueron completamente eliminadas o casi en de 2 a 3 semanas.

7) Entre los noventa y dos casos, el cierre de las cavernas ocurrió en 2 de cuatro a quince semanas después y reducción marcada en el tamaño de las cavidades se notó en 33 casos. La limpieza de los exudados ocurrio 17 veces.

8) En tres casos hubo disminución marcada y simultanea de varias cavidades dentro del mismo pulmón.

9) La extensión de la exudación ocurrió cuatro veces y fué mínima, una nueva cavidad solo aparente se observó en el lugar de una exudación previa a la terapéutica.

10) No hubo muertes debidas a la agravación de la tuberculosis.

11) Se vió mejoria o cura absoluta en casos de laringitis tuberculosa, otitis tuberculosa y glositis tuberculosa.

12) Los efectos tóxicos de la Marsilida y del Rimifón incluyen hiper-reflexia, contracción convulsiva de las piernas, constipación, vértigo y trastornos reflejos de micción.

13) No ocurrieron muertes debidas a la terapia.

14) Todos los pacientes fueron grandemente beneficiados por el tratamiento.

15) La investigación clínica de estos compuestos no ensayados previamente: la hidrazida del ácido isonicotínico (Rimifón) y su derivado isopropilo (Marsilida) revelan que son potentes agentes en el tratamiento de la tuberculosis humana.

RESUME

1) Quatre-vingt douze malades, atteints de tuberculose pulmonaire modérée ou très avancée, considérée comme certainement évolutive, et de forme ulcéro-caséeuse, ont été traités avec l'hydrazide d'acide isonicotinique ("Rimifon") et son dérivé isopropylique (Marsilid).

2) Tous les malades avaient une expectoration bacillifère, et étaien en pleine évolution avant le début du traitement. Quarante quatre d'entre eux étaient fébriles, et avaient un état général fortement atteint.

3) Les malades, répartis en deux groupes, furent traités par 2, 4 et 10 mg. de "Marsilid" par kilogramme, et par 4 mg. de "Rimifon" pendant un délai de 4 à 15 semaines.

4) Dans tous les cas, les signes d'intoxication et de fièvre disparurent complètement en deux à trois semaines. L'appétit augmenta la sensation de bien-être réapparut, mais ce qui fut le plus

remarquable, ce fut l'augmentation considérable du poids après une moyenne de 9 semaines de traitement.

5) Dans 25% des cas, les bacilles disparurent des crachats en 4 à 15 semaines de traitement et dans 28% des cas, il y eut une transformation des crachats habituellement très positifs en crachats inconstamment bacillifères.

6) Il y eut une disparition complète ou à peu près complète de la toux, et de l'expectoration en deux à trois semaines.

7) Parmi les 92 malades, dans deux cas on assista à la fermeture de la cavité en 4 à 15 semaines. Dans trente-trois cas, les dimensions de la caverne furent considérablement réduites, et 17 fois les infiltrations s'éclaircirent nettement.

8) Une diminution notable et simultanée de plusieurs cavités dans le même poumon fut constatée trois fois.

9) L'extension d'un infiltrat survint 4 fois, et fut très discrète. Dans un cas, une cavité apparut à la place où avait siégé un infiltrat avant la mise en train du traitement.

10) Il n'y eut pas de mortalité due à l'évolution de la tuberculose.

11) On constata la guérison ou une amélioration marquée dans des cas de laryngite tuberculeuse, d'otite tuberculeuse, et de tuberculose linguale.

12) L'action toxique du traitement par le "Marsilid" et le "Rimifon" peut être responsable d'hyper-réflectivité, de crampes dans les jambes, de constipation, de vertiges et de troubles de la miction.

13) Il n'y eut pas de décès dus à la thérapeutique.

14) Chaque malade a tiré le plus grand bénéfice du traitement.

15) Les investigations cliniques ont montré que ces nouveaux composés encore inusités, l'hydrazide d'acide isonicotinique ("Rimifon") et son dérivé isopropylique ("Marsilid") sont des agents efficaces dans le traitement de la tuberculose humaine.

REFERENCES

1 Fox, H. H.: "Synthetic Tuberculostats: III. Isonicotinaldehyde Thiosemicarbazone and Some Related Compounds," *XIIth International Congress of Pure and Applied Chemistry*, Sept. 9-13, 1951. Abstract of Papers, p. 299. Also, *Chem. and Eng. News*, Sept. 24, 1951, p. 3964.

2 Grunberg, E. and Schnitzer, R. J.: "Studies on the Activity of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice," *Quart. Bull.*, Sea View Hosp., 13:3, 1952.

3a Grunberg, E., Leiwant, B., D'Ascensio, I. L. and Schnitzer, R. J.: "On the Lasting Protective Effect of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis Infection of Mice," *Dis. of Chest*, 21:369, 1952.

b Zieper, I. and Lewis, R. A.: "Tuberculosis in a Macacus Rhesus

Treated with Isonicotinylhydrazine," *Quart. Bull.*, Sea View Hosp., 13: 12, 1952.

4a Benson, W. M., Stefko, P. L. and Roe, M. D.: "Pharmacological and Toxicological Observations of Hydrazine Derivatives of Isonicotinic Acid," *Am. Rev. Tuberc.*, In press.

b Lewis, R. A. and Zieper, I.: "Tolerance of Macacus Rhesus for Isonicotinylhydrazine," *Dis. of Chest*, 21:378, 1952.

5 Selikoff, I. J., Robitzek, E. H. and Ornstein, G. G.: "Toxicity of Hydrazine Derivatives of Isonicotinic Acid in the Chemotherapy of Human Tuberculosis," *Quart. Bull.*, Sea View Hosp., 13:17, 1952.

6 Robitzek, E. H., Selikoff, I. J. and Ornstein, G. G.: "Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid," *Quart. Bull.*, Sea View Hosp., 13:27, 1952.

7 Ornstein, G. G., Ulmar, D. and Dittler, E. C.: "A Clinical Classification of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 23:248, 1931.

8 Rubin, S. H., Drekter, L., Scheiner, J. and De Ritter, E.: "Determination of Blood Plasma Levels of Hydrazine Derivatives of Isonicotinic Acid," *Dis. of Chest*, 21:439, 1952.

9 Robitzek, E. H. and Selikoff, I. J.: "Hydrazine Derivatives of Isonicotinic Acid in the Treatment of Active Progressive Caseous-pneumonic Tuberculosis," *Am. Rev. Tuberc.*, In press.

10 Severinghaus, E. L., Cohen, S., Gans, R. H. and Lee, S. N.: "Nicotinamide Therapy of Lingual Changes in Tuberculous Patients," *Am. Rev. Tuberc.*, 62:360, 1950.

11 Tchertkoff, I. G. and Green, H.: "The Importance of Fever as a Diagnostic Sign of Intestinal Involvement in Chronic Pulmonary Tuberculosis," *Quart. Bull.*, Sea View Hosp., 7:231, 1942.

12 Selikoff, I. J.: "Diagnosis of Generalized Amyloidosis by the Congo Red Test: Definitive Diagnostic Criteria," *Am. J. Med. Sc.*, 213:719, 1947.

13 Gold, G.: Personal communication.

14 Bosworth, B. M., Wright, H. A. and Fielding, J. W.: "Marsalid in the Treatment of Tuberculosis Orthopedic Lesions," *Quart. Bull.*, Sea View Hosp., 13:52, 1952.

Determination of Blood Plasma Levels of Hydrazine Derivatives of Isonicotinic Acid

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Favorable results with Rimifon† (isonicotinyl hydrazide or Ro 2-3973) and Marsilid† (1-isonicotinyl-2-isopropylhydrazine or Ro 2-4572) as antituberculous agents in mice,[1,2] guinea pigs and rabbits,[3] monkeys[4] and humans,[5-8] have made desirable the development of methods for determining these compounds in body fluids. A procedure for blood plasma is presented in which the test compound is converted to isonicotinic acid and determined colorimetrically by the reaction with 10 per cent cyanogen bromide and ammonia described by Mueller and Fox[9] for nicotinic acid. A blank correction for non-specific color can be made by assay of a control sample taken before dosage. To eliminate the need for pre-dosage control the blank is better estimated by the reaction with 3 per cent cyanogen bromide and Metol, in which isonicotinic acid yields no color. Free isonicotinic acid is determined by assay of an unhydrolyzed aliquot of the plasma filtrate. Details of the assay are given below and results are presented of plasma studies after dosage to humans, dogs and mice.

Methods

Special Reagents: Cyanogen Bromide, 10 per cent: Dissolve 50 g. of crystalline cyanogen bromide (Eastman, stored in refrigerator) in 500 ml. of distilled water by shaking mechanically in a tightly stoppered bottle with a glass stopper. All operations involving cyanogen bromide must be performed in an efficient hood. No deterioration of this solution has been found at the end of one month. For 3 per cent solution dilute 3 to 10.

Buffered Ammonia Reagent: To a 1-L. volumetric flask containing about 500 cc. of distilled water add 87.0 g. of dipotassium phosphate (K_2HPO_4), reagent grade, and 107.0 g. of ammonium chloride, (NH_4Cl), reagent grade. Shake to dissolve the salts, then add 6.7 cc. of concentrated ammonium hydroxide (28 per cent),

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†These compounds were synthesized by Dr. Herbert H. Fox in the Roche Scientific Laboratories.

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reagent grade, and make to volume with water. Filter, if a sediment forms on standing.

Special Apparatus: Photoelectric colorimeter with 430 mu. filter. A Klett-Summerson colorimeter, Klett Mfg. Co., New York, has been used in the present studies.

Procedure: 1) *Determination by conversion to isonicotinic acid:* Pipette a 2 ml. aliquot of plasma from oxalated blood into an 18 x 175 mm. Pyrex test tube and add 16 ml. of water. Add 1 ml. of 10 per cent sodium tungstate followed by 1 ml. of 2/3 N H_2SO_4; stopper and shake vigorously after each addition. Place tube in a hot water bath at 90-100 degrees C. and cover with a glass bulb with a stirring rod attached as described by Klein et al.[10] Heat for 20 minutes with frequent stirring during the first five minutes and occasionally thereafter. Cool rapidly in a cold water bath and centrifuge five minutes at 2000 r.p.m. Tap the tube to dislodge particles clinging to upper walls and recentrifuge for five minutes. Pipette 15 ml. of the supernatant into a 50 ml. beaker and add 4 per cent $KMnO_4$ dropwise until a definite pink color persists.* Boil down over low heat on a hot plate to a volume of about 5 ml., adding 4 per cent $KMnO_4$ dropwise if necessary to maintain a pink color during evaporation. Add 1 per cent ascorbic acid solution dropwise until the pink color disappears, leaving the brown MnO_2 precipitate, and continue evaporation to dryness on a steam bath. Pipette 4 ml. of 0.2 per cent K_2HPO_4 into the beaker and stir vigorously for several minutes with a rubber policeman to dislodge the residue and effect solution of the isonicotinic acid. Pour this solution into a small centrifuge tube and centrifuge at 1500 r.p.m. for five minutes. Pipette 2 ml. of the clear supernatant into a colorimeter tube.

For colorimetry, add 2 ml. of buffered ammonia reagent and shake to mix. Then add 5 ml. of 10 per cent cyanogen bromide, stopper and mix immediately. Set the colorimeter with a 430 mu filter at zero absorbancy with a tube containing 2 ml. of water, 2 ml. of buffered ammonia reagent and 5 ml. of 10 per cent cyanogen bromide. Put the sample tube into the colorimeter within one and one half minutes after adding cyanogen bromide and read at maximum color intensity, usually between two and two and a half minutes. After $KMnO_4$ treatment the final solution is clear and colorless and no solution blank is necessary. (If NaOH is used for hydrolysis a solution blank is read after diluting 1 ml. with 8 ml. of water and setting the colorimeter at zero with a tube

*In the case of Marsilid only, which is hydrolyzed more easily than Rimifon, conversion to isonicotinic acid can be achieved in another way by adding 0.5 ml. of 8N NaOH and evaporating to dryness. In this case 3.5 ml. of 0.2 per cent K_2HPO_4 and 0.5 ml. of 8N H_2SO_4 are added before colorimetry.

containing only water. This reading is multiplied by two to compensate for the half volume taken and subtracted from the sample reading). Also colorize as above a 2 ml. aliquot of the standard solution of isonicotinic acid (10 micrograms).

Calculation: If:

A=reading of test solution

S=reading of standard isonicotinic acid (10 mcg.)

F=factor for converting weight of test substance to weight of isonicotinic acid (=0.898 for Rimifon and 0.688 for Marsilid),

Then:

$$\frac{\text{mg. of Rimifon or Marsilid}}{\text{100 ml. of plasma}} = \frac{A}{S \times F}$$

2) *Estimation of blank:* In addition to isonicotinic acid, the above method measures small amounts of non-specific, color-producing substances including nicotinic acid. Tests of many samples of human, dog and mouse plasma have shown these to be equivalent to 0.1 to 0.2 mg. of isonicotinic acid per 100 ml. of plasma. A correction for such non-specific color may be made by assaying a control blood taken before dosage or at least 48 hours after dosage. To eliminate the need for a pre-dosage control the non-isonicotinic acid color can be estimated by means of the reaction with 3 per cent cyanogen bromide plus Metol.[11] This reaction is commonly used for determining nicotinic acid, but gives no color with isonicotinic acid. A separate 2 ml. aliquot of the final test solution is required. Sufficient solution for this test may be obtained by taking 3 ml. of plasma plus 24 ml. of water; precipitate with 1.5 ml. each of 10 per cent sodium tungstate and 2/3 N H_2SO_4, and make the final dilution to 6 ml. rather than 4 ml. Then 2 ml. may be taken for colorimetry as usual and 2 ml. for estimation of the blank as follows. Pipette 2 ml. into a colorimeter tube, add 2.5 ml. of 2 per cent KH_2PO_4 and heat in a water bath to 70 degrees C. Add 0.5 ml. of 3 per cent cyanogen bromide and after exactly five minutes remove from the hot water bath and cool quickly by immersion in cold water. Add 5 ml. of freshly prepared 5 per cent aqueous Metol (Merck's Photol) solution, store in a dark place and read after 35 minutes with a 430 mu filter. Set the instrument at zero for this reading with a reagent tube in which 2 ml. of water are substituted for the 2 ml. of test solution. If this blank reading is equivalent to significantly more than 0.2 mg. of isonicotinic acid per 100 ml. of plasma, the administration of a high dose of nicotinic acid or nicotinamide may be indicated. For patients receiving no such vitamin supplement, readings by this method do not vary appreciably before and after dosage of Rimifon or Marsilid and are closely equivalent to read-

ings on undosed control samples by the 10 per cent CNBr method.

3) *Determination of free isonicotinic acid:* If free isonicotinic acid is present in the plasma, the value obtained above for Rimifon or Marsilid will be too high by an amount equivalent to this isonicotinic acid. The latter may be determined as described below and a corrected value for Rimifon or Marsilid calculated. However, since plasma levels of free isonicotinic acid are extremely small, even after the maximum doses of Rimifon and Marsilid used to date for tubercular patients, the following direct assay is not necessary for routine clinical testing. It may be applied in the case of tests involving very high dosages of Rimifon or Marsilid.

To determine free isonicotinic acid, pipette a 2 ml. aliquot of plasma from oxalated blood into an 18 x 175 mm. Pyrex tube. Add 2 ml. of water and precipitate proteins, heat, cool and centrifuge exactly as described above except that the total volume is 6 ml. instead of 20 ml. Pipette 2 ml. of the clear supernatant into a colorimeter tube for colorimetry as above with 10 per cent CNBr. Recentrifuge the remainder and pipette 1 ml. into a second tube. Add 8 ml. of water for a blank reading which is multiplied by 2 to correct for the half volume taken. If the net color is greater for a test blood after dose than for the corresponding control blood, the difference represents color due to free isonicotinic acid plus the increment due to the color given by Rimifon

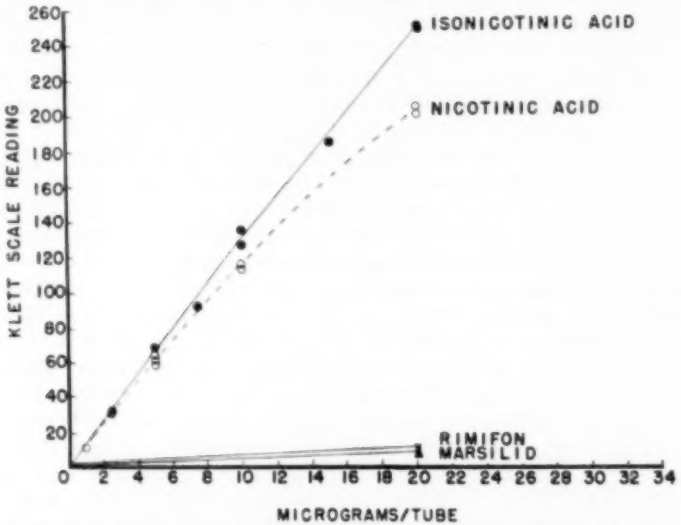

FIGURE 1: Relative intensities of maximum color at 430 mu after reaction with cyanogen bromide and ammonia.

or Marsilid per se. Since both compounds yield about 4 per cent of the color given by an equal weight of isonicotinic acid, a rigid calculation of results in this case requires solution of two appropriate simultaneous equations.

Results

Standard Curves: The spectrophotometric absorption curve of the reaction product of isonicotinic acid plus cyanogen bromide plus ammonia shows a peak at 434 mu as contrasted to 408 mu for the reaction product of nicotinic acid.[9] Relative readings in the Klett-Summerson photoelectric colorimeter with a 430 mu filter are shown in figure 1 for isonicotinic acid, nicotinic acid, Rimifon and Marsilid. Readings for nicotinic acid, which are only about 40 per cent of the peak values at 408 mu are slightly lower than for isonicotinic acid. The two isonicotinic acid derivatives yield only about 4 per cent of the color produced with an equal weight of isonicotinic acid. Hence, in order to obtain suitable color intensity in plasma assays, it is necessary to convert Rimifon and Marsilid to isonicotinic acid prior to colorimetry. This conversion is achieved by the permanganate treatment described. The effectiveness of this conversion is demonstrated by the fact that recoveries of increments of Rimifon and Marsilid added to human, dog and mouse plasma before protein precipitation, average consistently about 95 per cent. Recoveries of isonicotinic acid in the protein precipitation step are 95 to 100 per cent. The good

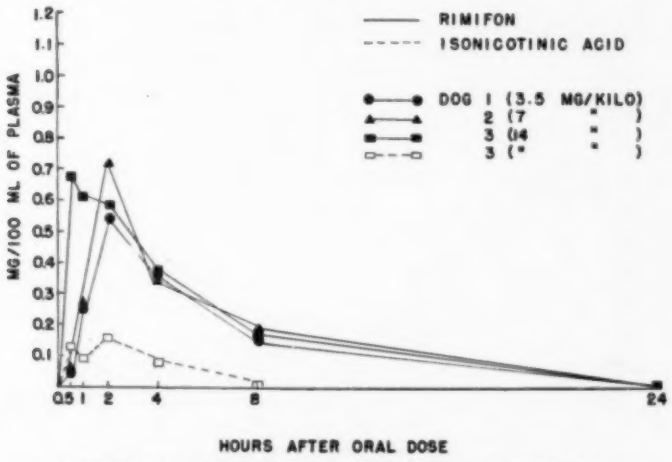

FIGURE 2: Dog plasma levels of Rimifon at intervals after graded oral doses.

reproducibility of the recovery values obviates the necessity for running an internal standard with every sample. Periodic spot checks of the recoveries are normally sufficient to confirm the performance of the method.

Dog Plasma Levels: Oral doses of 3.5, 7 and 14 mg. per kilogram of Rimifon were administered to normal dogs and blood samples withdrawn at intervals for 24 hours. Rimifon and isonicotinic acid were determined in plasma separated from the oxalated blood with the results shown in figure 2. The maximum plasma levels occur within two hours, the highest level showing the earliest peak. Plasma concentrations have dropped from the peak after four hours and return to zero within 24 hours. The levels of free isonicotinic acid are shown only for the dog receiving the 14 mg./kilo dose, and even at this high dose the top isonicotinic level is only 0.16 mg. per 100 ml. At the lower doses, isonicotinic acid levels are below 0.1 mg. per 100 ml.

The results of a similar experiment in which the same levels of Marsilid were given orally to three other dogs are shown in figure 3. The dog receiving the highest dose showed a peak plasma level in one half hour which dropped rapidly in the next few hours. The two dogs at the 3.5 and 7 mg. per kilo level did not show their maximum plasma level until two and four hours after dose. Maximum levels of Marsilid are somewhat higher than the corresponding levels of Rimifon, and after four hours this difference appears to be most pronounced at all three dose levels.

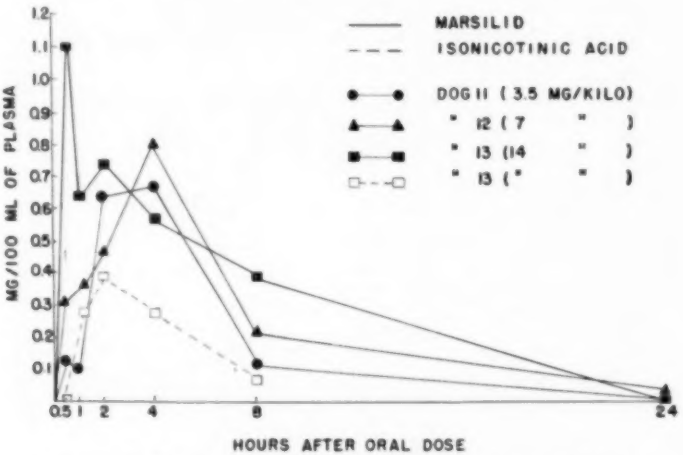

FIGURE 3: Dog plasma levels of Marsilid at intervals after graded oral doses.

Free isonicotinic acid levels in plasma are shown in figure 3 only for dog 13 at the 14 mg. per kilo dosage. At the lower dose levels, the amounts of free isonicotinic acid were much lower. Comparison of figures 2 and 3 shows that more isonicotinic acid is present in plasma after Marsilid than after Rimifon. It is likely that this difference is due to the fact noted above that Marsilid is hydrolyzed more readily than Rimifon to isonicotinic acid.

Mouse Plasma Levels: Pooled blood from groups of mice receiving 250 mg. per kilogram of Rimifon or Marsilid per day in the diet, as well as from an undosed control group, were assayed after sacrificing all animals at the same time. The Rimifon group showed 0.07 mg. of isonicotinic acid and 0.58 mg. of Rimifon and the Marsilid group 0.08 mg. of isonicotinic acid and 0.91 mg. of Marsilid per 100 ml. of plasma, all values being corrected for the control levels. The fact that blood levels are not high in relation to the doses fed may be due to the fact that the mice normally feed at night but were not sacrificed until 10 to 11 A. M. Hence, it is possible that the fairly long time interval between feeding and taking of the blood may have been responsible for the comparatively low blood levels.

Human Plasma Levels: Oral doses of Rimifon at various levels ranging from 1.1 to 3.4 mg. per kilo were administered to a number of tubercular patients at 9 A. M. Blood samples were withdrawn at intervals from one half hour to 24 hours after

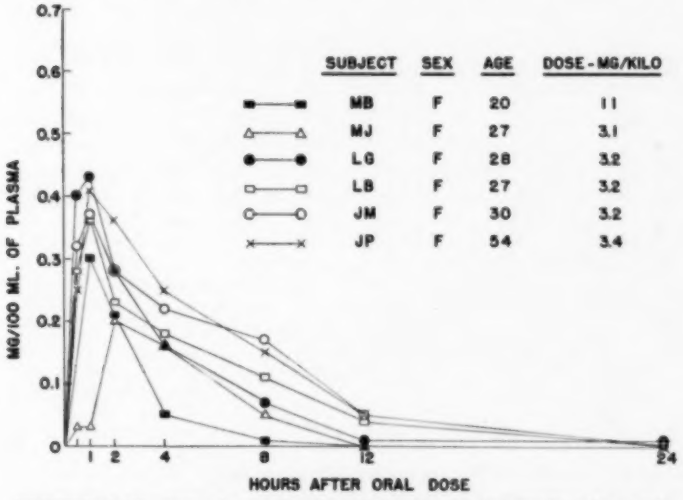

FIGURE 4: Human plasma levels of Rimifon at intervals after oral dosage to tuberculous patients.

dosage and transferred to oxalated tubes. Plasma was separated by centrifugation and assayed for Rimifon by the above procedures. The results are shown in figure 4. Maximum plasma levels appear to be achieved within one to two hours, following which they fall and return almost to zero within 12 hours after dose. The maximum level after the 1.1 mg./kilo dose is definitely lower than the peaks after the 3.1 to 3.4 mg./kilo doses. It may be noted, also, that after four and eight hours the higher doses maintain higher plasma levels. At all of these dosage levels the amounts of free isonicotinic acid in the plasma were so small (0.01 to 0.04 mg. per 100 ml.) as to be of questionable significance.

Figure 5 shows plasma levels of Marsilid after oral administration of doses ranging from 1.5 to 3.2 mg. per kilo. Again, the levels appear to reach a peak in one to two hours and to return to zero after 24 hours. In general, the higher doses yield higher maximal plasma levels, but there are appreciable differences between individuals at the same dose level. Concentrations of free isonicotinic acid in these plasmas range from 0.01 to 0.08 mg. per 100 ml., the highest value being found only at the 5 mg./kilo dose level. Comparison of figures 4 and 5 indicates a trend toward slightly later peaks and longer maintenance of plasma levels of Marsilid than of Rimifon, even though the doses of Marsilid were smaller.

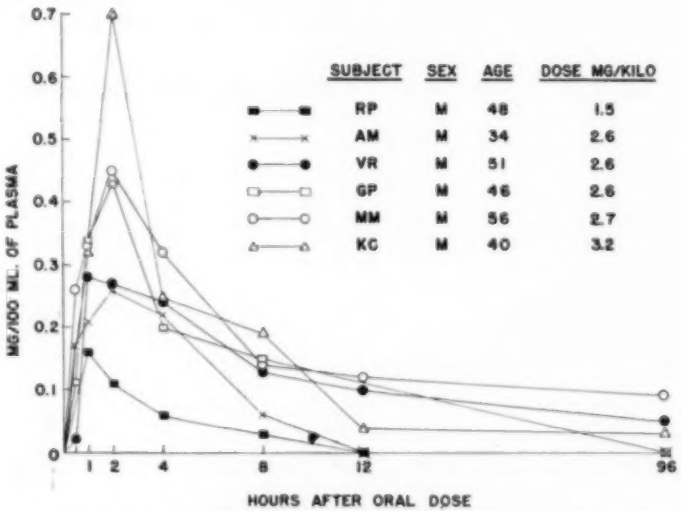

FIGURE 5: Human plasma levels of Marsilid at intervals after oral dosage to tuberculous patients.

Discussion

Since the analytical procedure does not involve separation of isonicotinic acid or its hydrazine derivatives from other substances such as nicotinic acid which contribute to the color produced in the cyanogen bromide-ammonia reaction, estimates of such non-specific colors were made in most of this work by assaying control samples of plasma before dosage. Experience with human, dog and mouse plasma has shown that undosed controls yield color readings equivalent to 0.1 to 0.2 mg. of isonicotinic acid per 100 ml. of plasma and are relatively constant under normal circumstances. Ingestion of large amounts of nicotinic acid or nicotinamide may lead to transitory rises in plasma levels which will interfere with isonicotinic acid determinations. The 3 per cent cyanogen bromide plus Metol reaction should be used to estimate the non-specific color blank in the absence of control plasma samples, and is the method of choice for routine work.

Both the dog and the human plasma studies show a rapid rise to maximum levels of both Rimifon and Marsilid. After the peak value is reached, which appears to occur within a few hours after an oral dose, the plasma levels of both substances decline rapidly and return to zero or to a very low level within 24 hours after dose. In the dog where equal doses of Rimifon and Marsilid were given, slightly higher plasma levels of Marsilid were found than of Rimifon, with the most consistent difference in the four hour samples. A similar trend toward higher levels of Marsilid than of Rimifon is seen in the human plasma data. Indications of a more rapid splitting of the isopropyl hydrazide (Marsilid) than of the hydrazide (Rimifon) were obtained in attempts to convert these derivatives to isonicotinic acid by acid or alkaline hydrolysis. The higher levels of free isonicotinic acid in dog plasma after Marsilid (figure 3) than after Rimifon (figure 2) may indicate a more rapid splitting of Marsilid in the animal body.

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SUMMARY

A colorimetric method is presented for the determination of blood plasma levels of isonicotinic acid and its derivatives, the hydrazide (Rimifon) and the isopropyl hydrazide (Marsilid). The

method is based on the reaction of isonicotinic acid with cyanogen bromide and ammonia. The hydrazide derivatives, which yield relatively slight color per se, are converted to isonicotinic acid by treatment of the protein-free plasma with permanganate. Plasma levels over a 24-hour period after a single oral dose are presented for dogs given 3.5, 7 or 14 mg. per kilogram of Rimifon or Marsilid and for humans receiving up to 3.4 mg. of Rimifon or 3.2 mg. of Marsilid per kilogram. In these limited trials maximum plasma levels are usually found within one-half to two hours after dose and decline rapidly. No significant amount of either compound was found in the plasma after 24 hours.

RESUMEN

Se presenta un método colorimétrico para la determinación del nivel en el plasma sanguineo del ácido isonicotínico y sus derivados, la hidrazida (Rimifón) y el isopropil hidrazida (Marsilida). El método está basado en la reacción del ácido isonicotínico con el bromuro de cinaógeno y amoniaco. Los derivados de la hidrazida que proporcionan un ligero matiz per se, son convertidos en ácido isonicotínico por el tratamiento de plasma libre de proteinas con permanganato.

Se presenta el nivel en el plasma después de un periodo de 24 horas después de una sola dosis oral que para los perros fué de 3.5, 7 ó 14 mg. por Kilogramo de Rimifón o de Marsilida y para los hombres de 3.5 mg. de Rimifón ó 5.0 mg. de Marsilida por Kilogramo. En estos ensayos limitados el nivel máximo de plasma ha sido encontrado en un periodo de media a cuatro horas después de la dosis y declino rápidamente. No se encontró en el plasma cantidad alguna considerable de ninguno de los dos compuestos después de 24 horas.

RESUME

Les auteurs presentent une méthode qui permet de déterminer dans le plasma sanguin le taux de l'acide isonicotinique et de ses dérivés, hydrazide ("Rimifon") et hydrazide isopropylique ("Marsilid"). La méthode est basée sur la réaction de l'acide isonicotinique, sur le cyanogène, le bromure et l'ammoniaque.

Les dérivés hydrazides qui en eux-même ne provoquent qu'une coloration très légère se transforment en acide isonicotinique par l'action du plasma protéinique avec le permanganate. Les taux plasmatiques pendant les 24 heures consécutives à une simple dose buccale ont été déterminés pour les chiens à qui furent administrés 3, 5, 7 ou 14 mg. par kilogramme de "Rimifon" ou de "Marsilid" et pour les hommes qui reçurent jusqu'à 3, 5 mg. de "Rimifon" ou 5 mg. de "Marsilid" par kilogramme. Dans ces expériences

limitées, la plus haute teneur du plasma a été constatée entre une demi-heure et quatre heures après l'absorption, avec diminution très rapide ensuite. Après un délai de 24 heures, on ne peut trouver dans le plasma de doses notables de l'un ou l'autre de ces composés.

REFERENCES

1 Grunberg, E. and Schnitzer, R. J.: "Studies on the Activity of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice," *Quart. Bull.*, Sea View Hosp., 13:3, 1952.

2 Grunberg, E., Leiwant, L., D'Ascensio, I. L. and Schnitzer, R. J.: "On the Lasting Protective Effect of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis Infection of Mice," *Dis. of Chest*, 21:369, 1952.

3 Steenken, W. Jr. and Wolinsky, E.: "Antituberculous Properties of Hydrazines of Isonicotinic Acid," *Am. Rev. Tuberc.*, In press.

4 Zieper, I. and Lewis, R. A.: "Tuberculosis in a Macacus Rhesus Treated with Isonicotinylhydrazine," *Quart. Bull.*, Sea View Hosp., 13:12, 1952.

5 Selikoff, I. J., Robitzek, E. H. and Ornstein, G. G.: "Toxicity of Hydrazine Derivatives of Isonicotinic Acid in the Chemotherapy of Human Tuberculosis," *Quart. Bull.*, Sea View Hosp., 13:17, 1952.

6 Robitzek, E. H., Selikoff, I. J. and Mamlok, E. T.: "Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid: Preliminary Report of Representative Cases," *Quart. Bull.*, Sea View Hosp., 13:27, 1952.

7 Selikoff, I. J. and Robitzek, E. H.: "Hydrazine Derivatives of Isonicotinic Acid in the Treatment of Active Caseous Pneumonic Tuberculosis," *Am. Rev. Tuberc.*, In press.

8 Selikoff, I. J. and Robitzek, E. H.: "Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid," *Dis. of Chest*, 21:385, 1952.

9 Mueller, A. and Fox, S. H.: "Determination of Nicotinic Acid in Pharmaceutical Products," *J. Am. Pharm. Assoc.*, Sci. Ed., 15:513, 1951.

10 Klein, J. R., Perlzweig, W. A. and Handler, P.: "Determination of Nicotinic Acid in Blood Cells and Plasma," *J. Biol. Chem.*, 145:27, 1942.

11 Dann, W. J. and Handler, P.: "The Quantitative Estimation of Nicotinic Acid in Animal Tissues," *J. Biol. Chem.*, 140:201, 1941.

Chloramphenicol† in the Control of Bronchopulmonary Suppuration*

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In chronic broncho-pulmonary suppuration purulent sputum, the result of bronchitis or pneumonitis, is a common presenting complaint. It may be a complication of chronic pulmonary disease, such as fibrosis and emphysema. Following bacteriologic and clinical arrest, it may be the basis for continued symptoms in tuberculosis, especially arising distal to broncho-stenoses. Finally, purulent sputum is seen in bronchiectasis, which despite advances in surgical technic continues to be a medical problem.

In a bronchographic survey of 383 patients at the Los Angeles County Hospital 161 proved to have bronchiectasis. Of these, 64 (39 per cent) proved to be bilateral and therefore unsuited for surgery unless extensive bilateral attack was to be considered. Further, 76 (48 per cent) were over 40 years of age. In addition, there must be added to the burden of medical management those patients with bronchiectasis in whom surgery has not eliminated all disease, and in whom residual dilations and bronchial stumps result in continuation of cough and purulent expectoration.

In 1946 one of us reported before this section from the bronchiectasis clinic of the Los Angeles General Hospital the successful control, over periods up to six months, of the purulent sputum and broncho-pulmonary complications of bronchiectasis by the daily administration of 1 gram doses of sulfa drugs. The limited range of antibacterial action, patient intolerance, adverse effects on the bone marrow, and the necessity of detailed laboratory control, limited this procedure's usefulness to 25 per cent of the 32 patients studied.

Since that time, the antibiotics, beginning with penicillin, later streptomycin, alone or in combination, systemically, or by aerosol have been employed with an enthusiasm proportional to the disappointment experienced when allergic reactions to the drugs, bacterial resistance, or over-growth of non-affected organisms have necessitated discontinuance of therapy.

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Without exploring in detail the shortcomings of therapy to date one might summarize as follows the characteristics of the ideal antibiotic for control of chronic broncho-pulmonary suppuration:

1) Safety, without detailed laboratory control.
2) Wide range antibacterial activity.
3) Persistence of effectiveness.
4) Convenience of administration.
5) Economy.

The advent of the so-called wide-spectrum antibiotics, of which chloramphenicol is the first to be synthesized, seemed to satisfy all these criteria except that of economy. This obstacle was made less formidable by an observation made by a patient with residual bronchiectasis who had frequent rises of temperature. It was noted that the 1.0 gram doses he took once or twice weekly not only controlled his fever, but also kept his sputum at a greatly decreased level. The same dosage was finally extended to a total of 62 patients who received the drug in doses of 1 gram two or three times weekly for periods of two to six and one-half months. Observations of the effect of this dosage constitute the basis for this report.

The concept of intermittent antibiotic therapy is not without precedent. In 1948 Parker and Luse observed that following a short exposure of a culture of staphylococci to penicillin a variable period of no growth (lag period) occurs.[1] During this period the damaged (if not destroyed) organisms fail to multiply and become susceptible to the continuing action of the host. It is this period of host action (and ineffective penicillin level) that allows for the discontinuous method of administration of penicillin.[2] Interrupted dosage with penicillin has been employed in a variety of infections.[3-5] Recent experiences with intermittent streptomycin therapy in pulmonary tuberculosis further suggest the utility of this concept.

A single oral dose of 1 gram of chloramphenicol is absorbed rapidly from the gastro-intestinal tract, producing an effective blood level in one hour (See Table I). This level persists for at least six hours which is as long as we have observed it. The drug also can be detected in traces in the sputum but not in levels that can be considered effective. For the determination on which these statements are based we are indebted to Dr. Eric Stern of the research staff of the Los Angeles Sanatorium.

Early in the study it became quite evident that the facilities at our disposal would not permit sufficient bacteriologic study to correlate clinical changes with factors of native bacterial susceptibility and acquired resistance. Early observations demonstrated we could not predict the clinical response by cultural studies,

since the same organisms were not always present in the same patient. Moreover, it was impossible to determine which organisms were responsible for symptoms. In addition we have had the experience of isolating from a surgical specimen organisms which were never found in the sputum. We, therefore have, in general, contented ourselves with smears and gram stains of the sputum during the periods of observation. These have not been without value, for we can say from these data that no radical change usually takes place in the flora. None of the overgrowth of gram negatives such as is seen in penicillin therapy was observed. It appears more likely that what we have accomplished is a depression of bacterial activity over a wide range without accomplishing disappearance of one group and overgrowth of another. In addition, no evidence of fungus invasion such as is sometimes seen in intensive therapy has been encountered.

The results are summarized as follows (See Table II):

Eleven patients with active or arrested tuberculosis, in eight of whom major bronchial stenosis was present received the drug as

TABLE I

Blood Levels of Chloramphenicol in Micrograms per CU.ML.

Patient	Hour: Zero	One	Two	Four	Six
C.M.	0	7	12	11.5	17
L.W.	0	17	34	50	24
I.C.	0	22	19	19	17
H.C.	0	44	39	39	39
B.B.	0	51	51	51	20
J.W.	0	65	65	80	60

TABLE II

Disease	No. of Cases	RESPONSE* Excellent No.	Pct.	Good No.	Pct.	Poor No.	Pct.
Emphysema and Chronic Bronchitis	13	4	31	3	23	6	46
Pulmonary Tuberculosis with Broncho-stenosis and Bronchiectasis	11	6	55	1	9	4	36
Bronchiectasis**	38	25	66	11	29	2	5
TOTAL	62	35	56	15	24	12	19

*Excellent—75 per cent reduction in sputum.
Good—50 per cent reduction in sputum.
Poor—0 to 50 per cent reduction in sputum.

**Twelve patients had received initial therapy with other antibiotics.

follows: two for two months, three for four months, and six for six months. Six experienced a 75 per cent or more reduction in sputum output. This effect was sustained throughout the period of treatment. One had 50 per cent reduction in sputum. Four had a poor result or no reduction in sputum or cough. Of these four, two had active pulmonary tuberculosis and most likely tuberculous bronchiectasis.

Of 13 with chronic bronchitis and emphysema, four received the drug for two months, four for four months, and five for six months. Excellent result, or a 75 per cent decrease in sputum occurred in four, a 50 per cent reduction or good result in three. In six the result was poor or unsatisfactory. In three of the six poor results, purulence of the sputum decreased but the total amount of sputum was unchanged.

In 26 cases of bronchiectasis treated intensively with chloramphenicol for one week followed by intermittent therapy for four months in 17, six months in nine, there were excellent results in 14 (75 per cent reduction), good results in 10 (50 per cent reduction) and poor or unsatisfactory results in two.

In 12 bronchiectatics with initial one week treatment by penicillin or penicillin and streptomycin, four received chloramphenicol for four months, and eight for six months. Excellent results were obtained in 11, and a good result in one. There was no failure.

At the conclusion of the study, 14 patients were given placebos, the remainder abruptly discontinued. Essentially all maintained their status for two months with a partial relapse occurring in most patients in the third month.

In the entire group only five who were finally classified as unsatisfactory had a good initial response. Thus clinically, evidence of acquired resistance appears infrequently and for the most part, a good initial response is sustained.

Complications

Gastro-intestinal complications such as nausea and diarrhea were not important side effects nor were skin reactions encountered with the doses employed.

Of a more serious nature, two cases of aplastic anemia were encountered. One of these was fatal, the other is in a chronic improving phase. These are being reported elsewhere. Chloramphenicol as the etiologic agent is strongly implicated although the evidence may not be considered absolutely conclusive.

Discussion

The experiences related here indicate that oral administration of chloramphenicol for both intensive therapy and prolonged

maintenance of bacteriostasis is an effective drug in chronic broncho-pulmonary suppuration. It fulfils the qualifications of easy administration, sustained wide-range effectiveness, and in the doses used, of economy. However, unless the blood reactions can be attributed to other causes, it does not fulfill the qualification of safety without detailed rigid laboratory control. Now that the effectiveness of intermittent dosage has been demonstrated, it remains to be seen if others of the wide spectrum antibiotics will better qualify in this and other requirements.

SUMMARY

1) Oral administration of chloramphenicol is effective in broncho-pulmonary suppuration.

2) Sustained improvement in the volume of purulent sputum is possible on intermittent dosage of the drug.

3) The drug fulfils essentially the requirements of an ideal antibiotic except that of safety without detailed laboratory study.

RESUMEN

1) La administración oral del cloramphenicol es efectiva en los casos de supuración broncópulmonar.

2) Es posible obtener una mejoría sostenida en el volumen del esputo purulento, con dosis espaciadas de la droga.

3) La droga satisface esencialmente los requisitos de un antibiótico ideal, excepto aquellos que se refieren al margen de sanguridad sin estudios detallados de laboratorio.

RESUME

1) L'administration par la bouche de chloramphenycol donne de dons résultats dans les suppurations broncho-pulmonaires.

2) Grâce à l'utilisation intermittente de la dose, on peut obtenir une diminution très nette de la quantité de crachats purulents.

3) Ce produit répond à ce qu'on demande à un antibiotique parfait quand on ne peut avoir des résultats de laboratories précis.

REFERENCES

1 Parker, R. F. and Luse, D.: "Action of Penicillin on Staphylococcus: Further Observations on the Effect of a Short Exposure," *Jour. of Bact.*, 56:75, 1948.

2 Eagle, H., Fleischman, R. and Musselman, A. D.: "Effect of Schedule of Administration on the Therapeutic Efficacy of Penicillin," *Am. J. Med.*, 9:280, 1950.

3 Tompsett, R., Timpanelli, A., Goldstein, O. and McDermott, W.: "Discontinuous Therapy with Penicillin," *J.A.M.A.*, 139:55, 1949.

4 Tumulty, P. A. and Zubroa, G.: "Pneumococcal Pneumonia Treated with Aqueous Penicillin at Twelve-Hour Intervals," *New Eng. Jour of Med.*, 239:1033, 1948.

5 Altemeier, W. A.: "Penicillin Therapy with Prolonged Interval Dosage Schedules," *Annals of Surg.*, 128:708, 1948.

Chronic Friedlander's Pulmonary Infection Treated with Chloromycetin; Case Report*

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The introduction in the past decade and a half of the sulfonamides and antibiotics in the treatment of bacterial infections has led to a variety of regimens in the therapy of Friedlander's pneumonia. Both the sulfonamides and streptomycin have been used with varying degrees of success.[1,2] More recently aueromycin has been employed with gratifying results.[3] Among the newer antibiotics, chloromycetin has, to our knowledge, never been previously reported as having been used in clinical Friedlander's infections. Gill,[4] in a recent report of the experience of the Pennsylvania Hospital with Friedlander's pneumonia, does not mention chloromycetin. Smadel,[5] in a review of the clinical usage of chloromycetin, fails to mention its use in Friedlander's infections. Hewitt and Williams,[6] reporting on their experience in the Massachusetts Memorial Hospital with chloromycetin in the treatment of various infections, present no data on the use of the antibiotic in Friedlander's infections. However, in vitro sensitivity studies of K. pneumoniae by the same investigators revealed that of 31 cultures, 25 were sensitive to less than five gamma per cc. of chloromycetin; three, to 5-10 gamma per cc.; one, to 10-50 gamma per cc.; and two to more than 50 gamma per cc.

Recently, we encountered a patient symptomatic with a chronic Friedlander's infection of the lungs, whose sputum cultures became negative, and who showed marked symptomatic improvement following chloromycetin therapy. Prior treatment with streptomycin and gantrisin had proved ineffective.

Case Report: F.H., a 58 year old white widow was admitted to the Queens General Hospital for epigastric pain of one week's duration. The pain was somewhat relieved by lying down, had no relation to meals and was associated with nausea. She reported a 25 pound weight loss over a period of a few years. Review of symptoms revealed chronic cough of many years' duration productive of a moderate amount of white mucoid sputum. No hemoptysis or night sweats. Physical examination revealed a moderately emaciated female with mild epigastric tenderness and bilateral medium-coarse, moist rales. Urinary examination was

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FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Chest roentgenogram taken on third hospital admission following penicillin therapy, but prior to streptomycin-gantrisin and chloromycetin therapy.—*Figure 2:* Chest roentgenogram following streptomycin and gantrisin therapy but prior to chloromycetin therapy.—*Figure 3:* Chest roentgenogram following completion of chloromycetin therapy.

negative. Blood count was as follows: Hgb. 11 Gms.; WBC 10,400 with 80 per cent polyneutrophiles. Erethrocyte sedimentation rate was 47 (corrected; Wintrobe). Sputum concentrates and cultures for tubercle bacilli were repeatedly negative. No smear or culture for predominating organism was recorded. Tuberculin test (1:1000) was positive. Gastric analysis revealed the absence of free HCL in the fasting specimen, but good acid response to histamine. Gastro-intestinal series was negative. Chest roentgenogram on October 14, 1947 was read as follows: "Lung fields are emphysematous. There is noted considerable accentuation of the lung markings in the right lower lobe. Lung structure in this zone has somewhat of a sponge appearance. The right costo-phrenic angle is blunted. Minimal calcific infiltration is present in the right lung apex." Repeat chest roentgenogram on November 7, 1947 showed no change. Her course was marked by afternoon rises in temperature to 100-100.5 degrees F. The abdominal symptoms responded to ant-acid therapy. No therapy was prescribed for the lung disease, and she was discharged on the 48th hospital day.

Two years later this patient was again admitted to the hospital for "weakness." For a few weeks prior to admission she had been troubled with an exacerbation of chronic cough. She had lost 20 pounds since the last admission. Anorexia was marked. A course of penicillin administered by nebulizer immediately prior to admission had not alleviated her symptoms. Past history on this occasion revealed an attack of "pleurisy" 25 years previously, and bilateral otitis media 12 years ago, which left her partially deaf. Physical examination revealed marked emaciation and bilateral, medium-coarse, moist rales, most marked on the right side of her chest. Urine examination was negative. Hgb. 12.9 Gms. WBC 16,500 with 82 per cent polyneutrophiles. Repeated smears and cultures of the sputum for tubercle bacilli were negative. Chest roentgenogram was reported as follows: "Both lung fields reveal generalized increase in broncho-vascular markings with enlargement of hili and pronounced accentuation towards the bases, much suggestive of honeycombing. There is obliteration of the right costo-phrenic angle due to thickened pleura." She ran a febrile course (to 102.5 degrees F.), which responded to penicillin. She was discharged 10 days following admission, moderately improved. No follow-up chest roentgenogram was obtained. Following discharge, reports of two sputum sultures were rereived, each positive for both B. Friedlander-group A and streptococcus viridans.

Two years later this patient was again admitted to the Queens General Hospital for chills, fever, headache and exacerbation of a chronic cough, of three day's duration. In the time that elapsed since her previous admission, she had continued to be troubled by a chronic cough productive of moderate amounts of mucoid, white sputum. Physical examination revealed a well-developed, markedly emaciated, elderly woman, who appeared to be both acutely and chronically ill. Temperature on admission was 101.6 degrees F. Fine, moist rales were present over both lung fields, anteriorly and posteriorly, most marked in the bases. Examination of the urine was negative. Hgb. 12.0 Gms. WBC 12,700 with 81 per cent polyneutrophiles. Fasting blood sugar 104 mg. per cent. Blod urea nitrogen was 10 mg. per cent. One blood culture was positive for staphylococcus aureus, coagulase negative. Following 48 hours of penicillin therapy (100,000 units every three hours), she evidenced moderate symptomatic improvement with a drop of temperature to 100.5

degrees F. Chest roentgenogram (Figure 1) taken at this time revealed the bilateral fibrosis and honeycombing seen on the film of two years ago, with superimposed diffuse soft infiltration in both lower lung fields. During the next three weeks five sputum specimens were reported as positive for B. Friedlander-group A in pure culture. She was therefore started on streptomycin, one gram daily in divided doses, plus gantrisin, one gram every six hours. Following three weeks of such therapy, the cough diminished, sputum production became minimal and her appetite improved. However, the temperature curve continued to show afternoon spikes to 100.5 degrees F., and multiple sputum cultures (gastrics) continued to be positive for B. Friedlander-group A. Repeat chest roentgenogram revealed no change (Figure 2). Sensitivity studies (in vitro) at this time proved that the organism was sensitive to chloromycetin in concentration of 0.2 gamma per cc.; to terramycin in concentration of 0.8 gamma per cc.; and to aureomycin in concentration of 5.0 gamma per cc. Chloromycetin was administered in doses of 500 mg. every six hours. During a three week course of therapy, her cough and sputum disappeared; there was marked improvement in appetite; and she volunteered a definite sense of well-being. However, her temperature continued to occasionally rise to 99.8 degrees F. in the afternoon. Sputum cultures (gastrics) obtained in the third week of therapy were negative. Two weeks following cessation of chloromycetin therapy, three consecutive sputum cultures (gastrics) proved again to be negative and the patient's remarkably improved clinical state continued. Chest roentgenogram at this time revealed complete regression of the soft infiltrative lesions and marked diminution of the bilaterally accentuated broncho-vascular markings (Figure 3). Repeated cultures for tubercle bacilli were negative.

Comment: This patient's course was unique for one with chronic pulmonary Friedlander's infection in that the pathology, as far as could be determined by chest roentgenogram, was that of fibrosis, emphysema and bronchiectasis rather than abscess formation. Although it has been claimed that the Friedlander bacillus is sometimes found in cases of bronchiectasis, where its significance is doubtful because it is only one of several organisms in the sputum,[7] it seems likely that in our patient this organism was actually an active agent in the production of symptoms. Firstly, the disappearance of the bacillus from the sputum was accompanied by marked clinical improvement; and, secondly, no other organism was cultured from the sputum. However, the establishment of an active Friedlander's infection super-imposed upon an old non-specific bronchiectasis cannot be ruled out.

The efficacy of chloromycetin in eradicating the Friedlander's infection, despite prior failure with streptomycin and gantrisin, is in accordance with the in vitro studies of Hewitt and Williams.[6]

ADDENDUM: Since acceptance of this paper for publication, Kirby and Coleman have reported successful treatment with chloromycetin of two cases of Friedlander's pneumonia.[8]

SUMMARY

A case of chronic pulmonary Friedlander's infection, successfully treated with chloromycetin, following failure of combined streptomycin and gantrisin therapy, is described.

RESUMEN

Se describe un caso de infección pulmonar crónica por bacilo de Friedlander, que fué tratado con éxito con cloromicetina, después de haber fallado la estreptomicina y gantrisina combinadas.

RESUME

Un cas d'infection pulmonaire chronique à bacilles de Friedlander a été traité avec succès par la chloromycétine. Ce traitement efficace avait été institué après l'échec d'un traitement combiné de streptomycine et de "gantrisine."

REFERENCES

1 Hyde, L. and Hyde, B.: "Primary Friedlander Pneumonia," *Am. J. Med. Science*, 205:660, 1943.
2 Wylie, R. H. and Kirschner, P. A.: "Friedlander's Pneumonia," *Am. Rev. Tuberc.*, 61:465, 1950.
3 Most, H.: "Recent Advances in the Therapy of the More Common Protozoan and Helminthic Infection of Man," *Bull. New York Acad. Med.*, 25:717, 1949.
4 Gill, R. J.: "Treatment of Friedlander's Pneumonia," *Am. J. Med. Science*, 221:5, 1951.
5 Smadel, J. E.: "Clinical Use of the Antibiotic Chloramphenicol (Chloromycetin)," *J.A.M.A.*, 142:315, 1950.
6 Hewitt, W. L. and Williams, B. Jr.: "Chloromycetin (Chloramphenicol) in the Treatment of Infections," *New England J. Med.*, 242:119, 1950.
7 Rosenthal, F. D.: "Streptomycin in Friedlander's Pneumonia," *Lancet*, 2:743, 1949.
8 Kirby and Coleman: "Chloromycetin in Two Cases of Friedlander's Pneumonia," *Am. J. Med.*, 11:179, 1951.

Pulmonary or Bronchial Lavage and Simultaneous Tomographies*

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Our experience in the Expert Committee which studied the pulmonary condition of employees of the Rio de Janeiro City Hall, in 1940, led us to an unfavorable opinion regarding the methods employed to determine the etiology and the clinical course of these lesions. As a result of mass radiology of the chest, a number with positive films needed diagnoses. According to the etiology or the activity of lesions, medical treatment and social service work would be started. Also prophylactic measures for contacts of the patients depended on an accurate diagnosis.

We found that in the majority of cases, roentgen examination without tomography, and bacteriological study of sputum or gastric lavage did not solve the problem. It was necessary to wait, keep the patient under a long surveillance, from three, six to 12 months, though it would be preferable to act quickly for the benefit of the patient and his contacts. The majority of the patients had scant or no expectoration. They were individuals who thought themselves healthy and had normal social activities. There were disappointing results from the direct examination of sputum and of gastric lavage. Sputum examination often was negative, as few organisms were present. Gastric lavage, which must be performed early after rising, when in total fasting, frequently failed at the tuberculosis dispensaries where these conditions could not be met.

In 1944, when we founded and supervised the Service of Pulmonary Diagnosis at the Sao Sebastiao Hospital, we became certain that it would not be possible to perform gastric lavage under good conditions, due to the great number of those who have shadows and the active life they lead. Then, we had the idea of replacing gastric lavage by tracheo-bronco-pulmonary lavage.

At that time, the value of gastric lavage was not doubted and many papers appeared on that subject. However, we found a discrepancy between mass fluorography, fast and precise, and bacteriological examination, slow and uncertain.

Our problem was the same, since we presented in 1936 our method of mass fluorography. It would be necessary to change

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the bacteriological technic to the situation created by the examination of apparently healthy persons.

But, between developing the idea of pulmonary lavage and its use in practice, there was a great problem, the general fear of inhalation pneumonia. We performed the first bronchial lavage in order to avoid the introduction of mouth organisms into the bronchial tree; and we published our first paper (Pulmonary Lavage in the Etio-pathogenic Evolutional Diagnosis of Tuberculosis; Revista Brasileira de Medicina, Rio, August 1944). The method did not cause the so-called inhalation pneumonia so we began the use of the transglotic technique submitting the patients to clinical and x-ray control. No pulmonary complications developed. Our publications in Revista Paulista de Tisiologia, May 1945, and Revista Medico-Cirurgica do Brasil, July 1945, detail our 400 first pulmonary lavages, 313 of which had complete study by bacteriological culture with the following findings:

Negatives (Tuberculosis)	265	
Positives (Tuberculosis)	48	(15.33 per cent)
Total lavages	313	

The positives for tubercle bacilli are thus distributed; direct examination 16 per cent; Loewestein culture 69 per cent; inoculation in guinea pigs 15 per cent.

Technique

The technique used on the Service for Pulmonary Diagnosis has undergone several modifications since 1944. The medical student G. Barroso, who did bronchial lavages on himself, contributed to improving the method.

We advise a previous cleansing of the mouth and the removal of dentures. The patient ought to be fasting and given no food or drink for two hours after the lavage, because of the anesthesia. The technician who performs the lavage must wear glasses and a gauze mask.

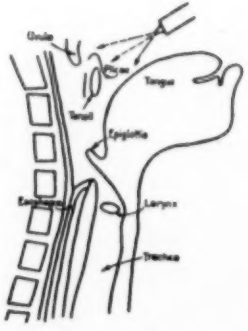
Every author describes his own method of performing the lavage; anesthesia (some don't use previous anesthesia), syringes or tubes, the amount of fluid, are used in accordance with individual choice. Our technique using local anesthesia, which results from our long experience with the method is as follows:

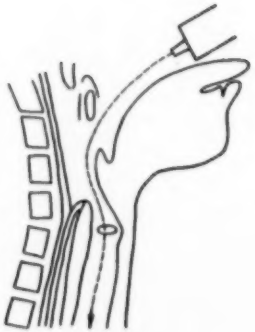
I. *Material Needed:*

1) Syringes of 2 cc. for the anesthesia and of 20 cc. for the introduction of physiological salt solution.

2) Small basins for collection of the anesthetics and salt solutions.

3) Large basins for collecting the specimen.





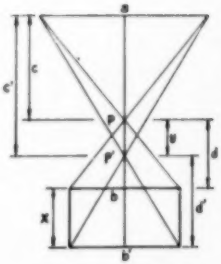


FIGURE 1 FIGURE 2 FIGURE 3 FIGURE 4

Figure 1: Bronchial lavage: anesthesia.—*Figure 2:* Introduction of the serum. — *Figure 3:* Principle of simultaneous tomographies. The films b and b' have their corresponding section p and p', during the same tube-film motion.—*Figure 4:* Cassette for simultaneous tomographies.

4) Sterilized gauze.

5) A 0.5 per cent solution of novotutocain, pantocain or tetracain in physiological salt solution and, finally, physiological salt solution.

II. *The Anesthesia:*

1) The patient must be in a sitting position, his head back slightly as if he were gargling.

2) Take a small portion of the anesthesic solution (2 cc. altogether) and preceed as follows:

a) Rinse the posterior part of the palate (one quarter of a cc.) in such a way as to reach the uvula, the anterior pillars, the tonsillar fossae, and the base of the tongue; wait one minute; repeat the operation and wait another minute;

b) one more application of anesthetic (one quarter of a cc.), this time asking the patient to utter the syllable *ha* three times, thus permitting the anesthetic to take a downward course and rinse the pharynx; another one minute intermission;

c) pull the tongue forward in such a manner as to reach the posterior wall of the pharynx directly; then pour in one quarter of a cc. of anesthetic; the patient must breathe slowly; repeat this procedure three times.

Advice: Have the patient spit out his saliva; the time between applications will permit the doing of several lavages simultaneously.

III. *Introduction of the Saline Solution:*

1) Touch the uvula with the syringe, also the pillars and the pharynx, in order to confirm the effectiveness of the anesthesia. In case it is not sufficient one should repeat the operation *b* and *c*.

2) Again pull the tongue forward, while the patient breathes slowly and continuously; then introduce from 10 to 20 cc. physiological salt solution into the pharynx; introduce slowly and stop a moment when the patient wants to cough; such an introduction is made from the base of the tongue.

3) When rhonchi are heard; ask the patient to cough and spit into the large basin; the total procedure takes from 10-15 minutes.

Contraindications

No accident has been observed. In no case have we had spread of disease by inhalation. There are, however, contraindications such as:

1) Sufficient sputum which renders the lavage unnecessary.

2) Pulmonary disease accompanied by general symptoms, fever included. It is better to wait until such symptoms disappear.

3) Signs of asthma or asthmatic bronchitis. Patients who have bronchial spasm do not tolerate pulmonary lavage.

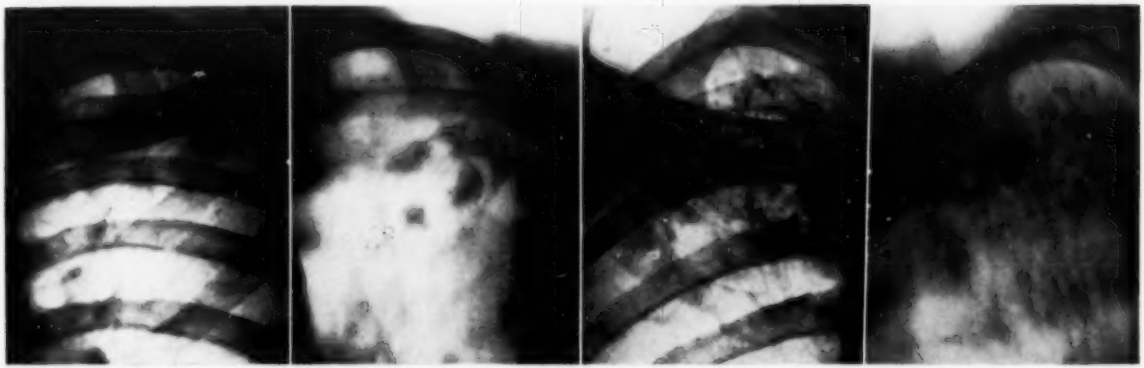


FIGURE 5 FIGURE 6 FIGURE 7 FIGURE 8

Figure 5, Case A: Radiograph. Slight shadow.—*Figure 6, Case A:* Tomography. Residual lesions (fibrous and calcified). B. L. negative.—*Figure 7, Case B:* Radiograph. Disseminated nodules.—*Figure 8, Case B:* Tomography. Residual lesions (fibrous and calcified). B. L. negative.

FIGURE 9 FIGURE 10 FIGURE 11

Figure 9, Case C: Radiograph. Slight shadow.—*Figure 10, Case C:* Tomography. Reticulated aspect (emphysema). B. L. negative.—*Figure 11, Case D.:* Tomography. Fibrous net and emphysema. B. L. negative.

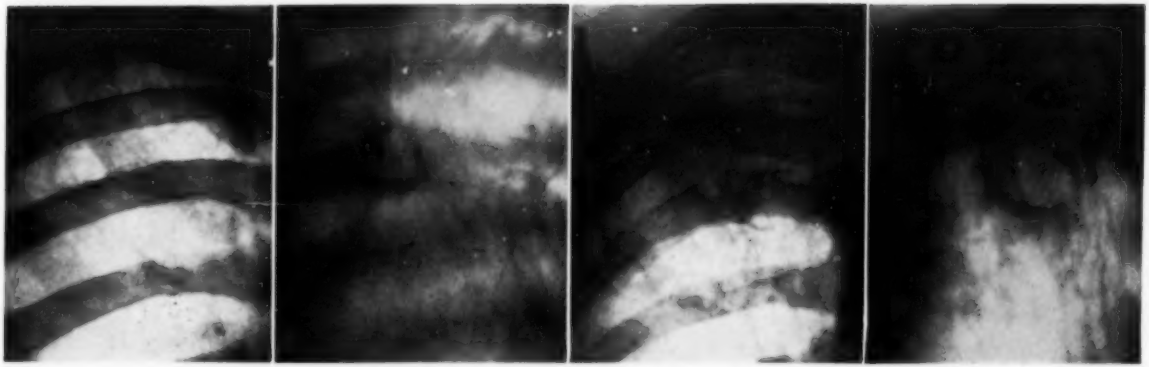


FIGURE 12 FIGURE 13 FIGURE 14 FIGURE 15

Figure 12, Case E: Radiograph. Ring shadow not evident (hidden cavity).—*Figure 13, Case E:* Tomography. Cavity well visible. B. L. positive.—*Figure 14, Case F:* Radiograph. Diffuse consolidation (hidden cavity).—*Figure 15, Case F:* Tomography. Sharply outlined cavity. B. L. positive.

4) Children who cannot expectorate.

5) Patients who have dyspnea from respiratory or cardiac causes.

Indications

The main indications of pulmonary lavage can be summarized as follows:

1) To determine etiology in patients with pulmonary lesions of unknown nature, generally revealed by mass chest fluorography.

2) To determine activity. Patients with specific lesions whose activity must be definitely determined.

3) Control of therapy during the treatment of pulmonary tuberculosis.

Besides the tubercle bacillus study, bronchial lavage permits the study of the bronchial secretion for many broncho-pulmonary diseases, bronchiogenic carcinoma included. Early treatment depends on early etiologic diagnosis; then, one can understand the value of pulmonary lavage performed on all such lesions, suspected of being tuberculous.

Statistics

It is not possible to state the exact number of bronchial lavages performed in Brasil, as the method is widely employed in many specialized services, from which statistics have not been published. Results obtained at the Diagnosis Pulmonary Service (Rio) and at the Clemente Ferreira Institute (Sao Paulo) are as follows:

Rio, 1944-1949

Number	Negative	Positive (Tuberculosis
Total 1,706	1,333	373 (21.86 per cent)

Sao Paulo, 1945-1949

Number	Negative	Positive (Tuberculosis
Total 4,600	3,851	749 (16.2 per cent)

General Statistics

Number	Negative	Positive (Tuberculosis
Total 6,306	5,184	1,122 (17.79 per cent)

The data from the Clemente Ferreira Institute were collected by R. Brandi, to whom we express our thanks. In Rio, all dispensaries included, bronchial lavages exceed 4,000.

Gastric and Pulmonary Lavages

Several authors used both techniques in a small number of cases, in order to compare the efficiency of each. Such studies are now less important, because of the advantages of the broncho-pulmon-

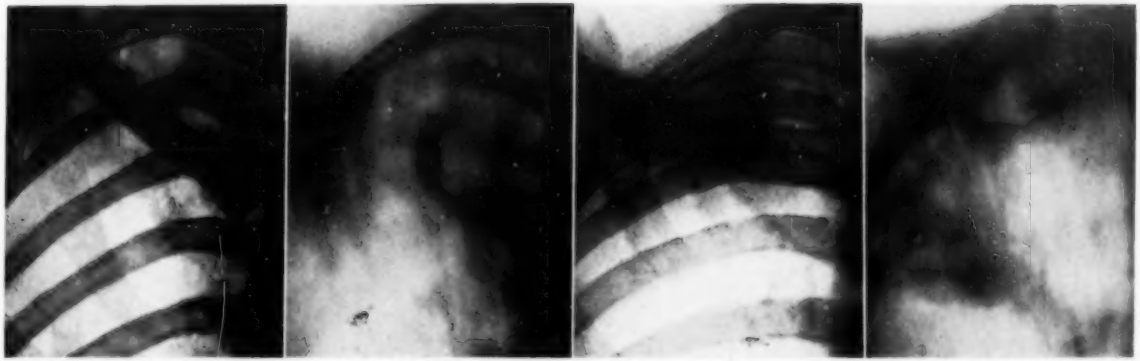


FIGURE 16 FIGURE 17 FIGURE 18 FIGURE 19

Figure 16, Case G: Radiograph. Spread shadow (hidden cavity).—*Figure 17, Case G:* Tomography. Thick wall cavity. B. L. positive. —*Figure 18, Case H:* Radiograph. Diffuse shadow (occulte cavity). — *Figure 19, Case H:* Tomography. Cavity with secretion (liquid level). B. L. positive.

ary lavages, the rapidity in great series, and it's efficiency as proved by the results of laboratory studies.

The first study was made by R. Fernandes on 18 patients with tuberculosis, apparently healed, on whom the pulmonary lavage proved to be more efficient:

	Gastric	Pulmonary
Negative	17	10
Positive	1 (5.55 per cent)	8 (44.44 per cent)

Here is a comparative study by A. P. Heudtlass, J. A. Marti and A. Adamo (La Prensa Medica Argentina, July 1945):

	Gastric	Pulmonary
Negative	70	66
Positive	0 (0 per cent)	4 (5.75 per cent)

Those same 70 patients were examined by both methods. The authors conclude:

"We hold the same opinion as Dr. de Abreu, with reference to the easy technique, the immediate and remote lack of complications, as well as to the superiority of the pulmonary lavage. This new method (best as to technic and results) must replace gastric lavage as a means of diagnosis, of treatment and, finally, of helping to dispose of the case."

However, R. Brandi, at the Clemente Ferreira Institute, during the year 1947, used both techniques on *different individuals*, having performed 436 gastric and 983 pulmonary lavages. The positive results were respectively 18.6 and 17.2 per cent. The author thinks that the efficiency of these methods presents no remarkable difference. He did not go on with the comparative study, for, in 1948 and 1949 he only did pulmonary lavage.

In our opinion gastric lavage, though performed at a hospital, with the patient fasting, does not seem to show the same efficiency as pulmonary lavage. At the dispensaries, however, where the patients with initial or discreet lesions are examined, the greater efficiency of the new method leaves no doubt.

Several authors agree with our opinion. Gernez-Breton and Mereau (Tuberculosis Pauci-bacillaire Diagnosis by the de Abreu Method, Revue de la Tuberculose, 1946, page 740):

Number	— — P O S I T I V E — — Gastric	Pulmonary
23	16 (69 per cent)	20 (87 per cent

A. Garaventa (The Broncho-pulmonary Lavage in the Pauci-baccilaire Tuberculosis Diagnosis, Arch. E. Maragliano di Patologia e Clinica, November 1949):

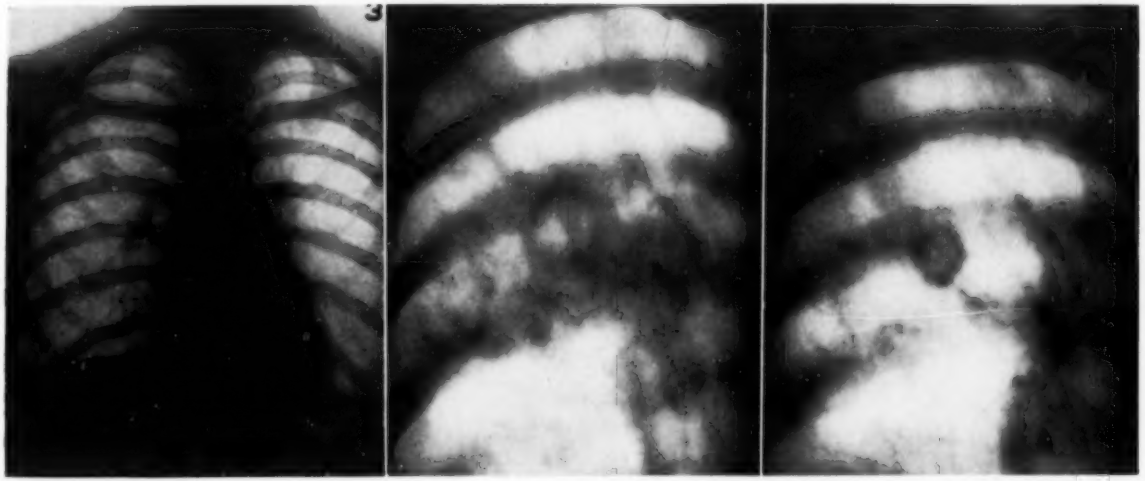


FIGURE 20 FIGURE 21 FIGURE 22

Figure 20, Case J: Slight shadows under the right clavicle.—*Figure 21, Case J:* Tomography. Exudative infiltration and cavity.—*Figure 22, Case J:* Tomography. Another small cavity.

Number	— — POSITIVE — — Gastric	Pulmonary
20	2 (10 per cent)	5 (25 per cent)

"Bronchial lavage has a definite place among the tests to detect tubercle bacilli. In patients suspected of pulmonary tuberculosis by x-ray, diagnostic bronchial lavage should be routine" (M. M. Bueno, Diagnostic Bronchial Lavage in Tuberculosis, Diseases of the Chest, October 1949).

X-Ray and Pulmonary Lavage

Roentgen examination, individual, not collective, based on tomography, is important to study the etiology and problems of progression of lesions. Each case needs a special technique; several exposures, horizontal or obliques and tomographies. The simultaneous tomographies permit one to obtain three sectional cuttings during a single tube-film motion. Such method has been described by us at the Clinica Tisiologica, Rio, July 1947. This roentgen examination well performed reveals the structure of the lesions, segmental or non-segmental, the presence of hidden cavities and of fibrous residues with calcareous nodules. We do simultaneous tomograms on films 13 x 18 cm. in almost all cases.

The residual lesions frequently appear like a thin, reticulated shadow, in which small areas of emphysema are surrounded by fibrous bands and calcareous deposits (tomography). We may see, also, a single residual cavity with very thin walls, in which the lavage has been repeatedly negative.

Generally there is an agreement between the x-ray interpretation and the results of the pulmonary lavage. Usually the exudative or excavated lesions give a positive bacteriological culture. When there is x-ray bacteriological disagreement, we repeat the bronchial lavage and recommend guinea pig innoculation, besides the usual culture.

The roentgen examination, based on tomography, is the most important. The x-ray impells the medical investigator to study the lesions: Their nature, extension, anatomical location and activity. However, pulmonary lavage is very important to determine if bacilli are excreted and thus to control the clinical and roentgenological findings.

Pulmonary Lavage in Series

The importance of the method lies in the possibility of obtaining broncho-pulmonary secretions rapidly, on quite a number of patients. We always do serial lavage, by starting the anesthesia on five to six patients successively: in this way, we can get anesthesia, without waste of time.

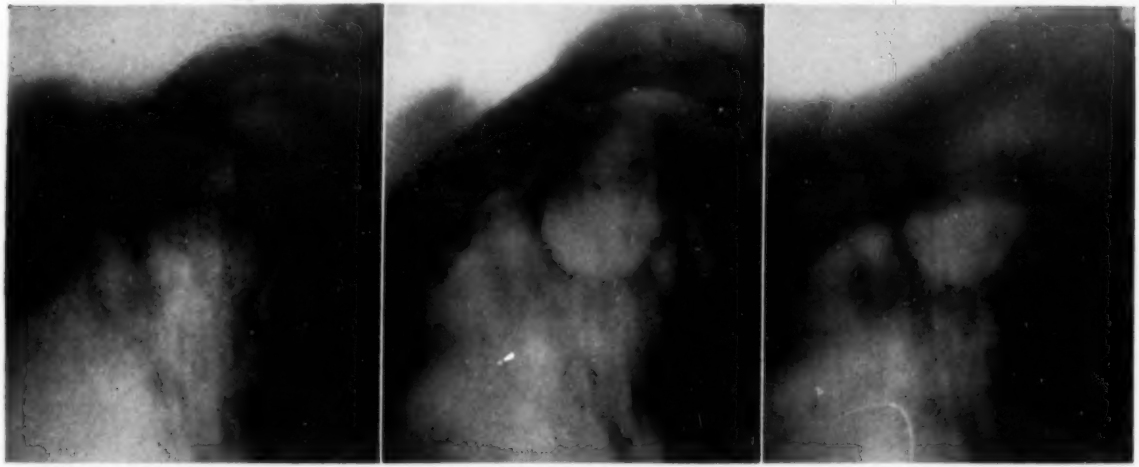


FIGURE 23 FIGURE 24 FIGURE 25

Figure 23, Case K: Simultaneous tomographies. Anterior section.—*Figure 24, Case K:* Simultaneous tomographies. Median section. Cavity well visible.—*Figure 25, Case K:* Simultaneous tomographies. Posterior section.

We know that the general use of pulmonary lavage has been motivated by the simplicity of the procedure. The collecting of tracheo-bronchial secretions in patients discovered by mass fluorography of the chest, confirms the status of a great number of pulmonary lesions.

Negative and Positive Lavages (B L)

A) *Negative Lavage:*

If the bronchial lavage is negative and tomography reveals fibrous or fibrous-calcareous lesions, surrounded by localized emphysema, there is x-ray and bacteriological agreement. Probably the lesions are residual. In the case of atypical shadows, one must proceed with the differential diagnosis: non-specific inflammatory process, bronchiectasis, cysts, tumors, etc.

If there is any x-ray sign of active tuberculosis (presumable exudative alveolitis or cavity), another pulmonary lavage is recommended. The second lavage, with culture and guinea pig inoculation, generally confirms the activity of the lesion.

B) *Positive lavage:*

In all cases with positive lavage, we observe x-ray and bacteriological agreement; tomography reveals exudative or fibrous-exudative infiltration and, frequently, the presence of cavities.

When there is no agreement (very rare occurrence) we must repeat the lavage. A normal x-ray film or a discreet lesion of residual appearance (tomography), generally has a negative lavage.

SUMMARY

As a result of mass fluorography, abnormal pulmonary shadows are detected. The etiology or activity of these lesions must be determined. There are cases of residual or progressive tuberculosis; there are cases of other diseases. The diagnosis directs the medical advice, prompt treatment before symptoms develop as well as prophylaxis, and administrative measures.

The author described in 1944 a new method of pulmonary lavage (bronchial or tracheo-bronchial), that replaces gastric lavage with advantage. In those people with shadows it is useful to employ localized tomography for the study of lesion structure. Simultaneous tomographies is the better method. In those with slight bronchial secretion, generally paucibacillaire, or without secretion, the author performs pulmonary lavage for bacteriological study.

Statistics of 6,306 pulmonary lavages is given, in which the incidence of active tuberculosis reaches 17.79 per cent.

The problem of the nature and the activity of the pulmonary

FIGURE 26 FIGURE 27 FIGURE 28

Figure 26, Case L: Simultaneous tomographies. Anterior section.—*Figure 27, Case L:* Simultaneous tomographies. Median section. Cavity well visible.—*Figure 28, Case L:* Simultaneous tomographies. Posterior section.

lesions has assumed social significance and calls for new and efficient administrative procedures. Central laboratories doing x-ray and bacteriology, able to perform a large number of tomographies, cultures and inoculations, are the indispensable complement of mass fluorography.

RESUMEN

Como resultado de la fluorografía en masa se descubren sombras anormales pulmonares. La etiología o actividad de estas lesiones debe determinarse. Hay casos de tuberculosis residual o progresiva y hay casos de otras enfermedades.

El diagnóstico conduce a consejo médico y tratamiento inmediato antes de que los síntomas se presenten y así mismo permite el empleo de medidas profilácticas y administrativas.

El autor describió en 1944 un método nuevo de lavado pulmonar (bronquial y traqueobronquial) que substituye al lavado gástrico con ventaja.

En los sujetos con sombras es útil el uso de la tomografía local para el estudio de la estructura lesional. Las tomografías simultáneas son el método mejor. En aquellos con escasa secreción bronquial, generalmente paucibacilares o sin secreción, el autor hace el lavado pulmonar para estudio bacteriológico.

Se presenta la estadística de 6,306 lavados pulmonares en los que la incidencia de la tuberculosis alcanza 17.19 por ciento.

El problema de la naturaleza y la actividad de las lesiones pulmonares, ha asumido significación social y requiere medidas administrativas nuevas y eficientes.

Un complemento indispensable de la fluorografía en masa es la creación de laboratorios centrales que hagan gran número de tomografías, cultivos e inoculaciones.

RESUME

Le résultat de la radiographie systématique est la mise en évidence d'ombres pulmonaire anormales. Il est nécessaire de déterminer quelle est l'étiologie et l'activité de ces lésions. Dans certains cas, il s'agit de séquelles de tuberculose ou de tuberculose évolutive, dans d'autres cas, la tuberculose n'est pas en cause. Le diagnostic est nécessaire pour permettre un traitement rapide avant que les symptômes ne prennent trop d'extension, aussi bien que pour mettre en oeuvreles mesures prophylactiques et administratives.

L'auteur a décrit en 1944 une nouvelle méthode de lavage pulmonaire (lavage bronchique ou trachéobronchique) que remplace avantageusement le tubage gastrique. La tomographie est indispensable dans ces cas pour étudier la lésion. Les "tomographies simultanées" réalisent la meilleure méthode. Chez les individus

qui ont une sécrétion bronchique légère, et généralement pauci-bacillaires, et qui n'ont aucune sécrétion, l'auteur utilise le lavage bronchique pour faire les recherches bactériologiques.

Une statistique de 6,306 lavages pulmonaires montre qu'une tuberculose active a été découverte dans 17.9% des cas.

La connaissance de la nature et de l'activité des lésions pulmonaires entraine des mesures sociales et administratives. Des laboratoires centraux, équipés pour la radiologie, la bactériologie et capables de fournir un grand nombre de tomographies, de cultures et d'inoculations sont les compléments indispensables des examens radiologiques systématiques.

Discussion

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This paper consists of two portions: first, obtaining tubercle bacilli from a patient who has no sputum; second, the visualization of early tuberculosis by body section radiography. Dr. de Abreu has made a very significant contribution to the diagnosis and care of the tuberculosis patient.

Regarding lavage, I want to subscribe wholeheartedly to this idea and to the method that Dr. de Abreu presents what he calls "bronchial lavage." A large amount of literature on this subject has developed since 1944. It is called "pulmonary lavage," "bronchial lavage," and we choose to call our procedure "tracheal lavage," as that is what we really do. At any rate, the procedure is essentially the same. It has been just two years since we have done a gastric lavage in our office or in any of our own hospital services, except on a small child. Tracheal lavage is innocuous, it is direct, it can be done at any time, is simple, and the results of culture or guinea pig inoculation are even more productive with this procedure in finding tubercle bacilli than they are with gastric lavage. When we started out to use this, we did it, not because we were interested in proving this procedure itself was any better in finding tubercle bacilli than was gastric lavage but because it was so much more convenient in office practice, for example, and so much more satisfactory as a hospital routine that we wanted to know if it was just as good. As a matter of fact, it has proved to be better. We got Drs. Wardrip and Scarborough interested in this procedure at Alum Rock Sanatorium in San Jose and they published their results in April 1949. Dr. Gwyn Roberts supervised their bacteriology. I asked Dr. Wardrip to give me his most recent results and up-to-date they are as follows:

Since October 8, 1948, they have done 120 tracheal washes and cultures—91 of these were positive and 29 were negative by culture. This means little unless the cases are classified, of course, except that it is innocuous.

Our own use of the procedure is even more extensive. We have done 359 different patients with no untoward results from the procedure. We use this to determine whether a patient is eliminating tubercle bacilli from the tracheobronchial tree for three major problems. First, as a matter of diagnosis. Is a lesion tuberculous and is it active? The definite finding of tubercle bacilli will ordinarily settle that question. Secondly, in primary pleural effusion or in a recent convertor from negative to positive tuberculin, who has no visible pulmonary x-ray lesion of tuberculosis. Some of these patients will show a positive tracheal lavage, in which case we believe that they must have active, definitive treatment. Thirdly, in collapse therapy to determine when (after sputum ceases to be produced) tubercle bacilli can still be obtained.

I noted in a preliminary draft of the new edition of Diagnostic Standards, which will soon be off the press, tracheal lavage is given as an alternative procedure to gastric lavage. Dr. Abreu again deserves a great deal of credit for the development and popularizing of this procedure which in our own hands after two years on 359 patients has proved to be an invaluable method without risk.

The second part of Dr. de Abreu's paper deals with the use of tomograms. While our own experience with this goes back over many years, it has not been extensive. I believe, as a matter of fact, that we fail to use the principle of body section radiology to get out of it all that is possible for the diagnosis of or in the localization of pulmonary shadows. However, I am still puzzled regarding the real interpretation of tomograph films. Some post mortem studies that have been done show 50 per cent error both ways between the shadows as shown on the tomograph films and the actual pathology as revealed at autopsy.

There is another interesting approach to developing this correlation, however, through the use of the recent increase of excision therapy. In those patients who have surgical removal of a segment, a lobe, or an entire lung, we have an excellent opportunity to relate a tomographic x-ray study to the pathology. Studies of this kind should be fruitful.

Recently, our surgeons removed an upper lobe because tomograph films showed a residual cavity and on sectioning the specimen no cavity whatever could be demonstrated. Tomography deserves, however, a great deal more study with pathological correlation.

Tuberculous Empyema Treated with Streptokinase-Streptodornase: Report of a Case with Cure

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The value of streptococcal concentrates, containing streptokinase and streptodornase in the treatment of pyogenic empyema has been well demonstrated by Tillett[1] and his associates. These two substances are produced from cultures of certain strains of beta hemolytic streptococci (Group A). Streptokinase is a catalytic agent which has the property of bringing about the liquefaction of fibrin. Streptodornase is an enzyme capable of dissolving desoxyribonucleo proteins and desoxyribonucleic acid. These latter substances are present as an exudative coating over tissue surfaces in the presence of infection. When the enzymes are introduced into the pleural cavity in empyema, rapid favorable changes take place as both blood clots and pus are dissolved. The exudate is markedly thinned and can be readily removed by needle aspiration. The enzymes are apparently non-toxic to normal healthy tissue. The use of streptokinase-streptodornase is now generally accepted as a specific form of therapy for pyogenic empyema and as an adjunct to surgical procedures in the pleural cavity.

Tuberculous empyema presents a more difficult problem, since the lung and pleura are usually involved with irreversible pathological changes which make expansion and proper functioning of the lung impossible. However, it appeared theoretically possible that if tuberculous empyema were treated at an early stage, before irreversible changes took place, that a cure might be obtained. This report deals with the successful treatment of a patient with tuberculous empyema by use of streptokinase-streptodornase.

Case Report

M.L., a 28 year old white male whose past history was negative, developed a sudden hemoptysis and fever on February 16, 1946. Examination showed him to have a left apical exudative lesion. Sputum was positive for tubercle bacilli. Because of the severity of the hemoptysis, left artificial pneumothorax was induced. On June 24, 1946 he developed a perirectal abscess which was drained. On July 3, 1946 he suffered a tuberculous otitis media and a left mastoiditis, which required extensive drainage. On July 21, 1947 he entered Fitzsimmons Hospital and remained until December 28, 1947. During this time he received streptomycin for the first time, both parenterally and locally, to the middle ear and drain-

*From the Department of Internal Medicine, Washington University School of Medicine.

ing mastoid sinus. Both lesions apparently healed following his return from the sanatorium. The pneumothorax was continued, 300 to 400 cc. at weekly intervals. From the start of the pneumothorax therapy, pleural fluid was present, and from time to time had to be aspirated. On June 28, 1948 the fluid was clear but showed tubercle bacilli. On October 15, 1949 the introduction of 200 cc. of air produced a positive pressure. On November 11, 1949 considerable fluid had developed and introduction of 50 cc. of air caused a positive pressure. On December 7, 1949 aspirated fluid was milky and showed tubercle bacilli. Air could no longer be introduced and the pneumothorax was discontinued. From that date up to March 27, 1950, thick purulent fluid was repeatedly removed from the left pleural cavity. Tubercle bacilli were present, but cultures for pyogenic organisms were negative. The lung remained fixed from November of 1949 to March 27, 1950 (Figure 1).

On March 27, 1950, 100,000 units of streptokinase and 40,000 units of streptodornase were instilled into the left pleural cavity. The following day, 300 cc. of yellowish purulent fluid were removed. The patient ran a fever up to 102 degrees F. for one week. Five days after the introduction of the enzymes, 150 cc. of yellow pus were removed and it was then noted for the first time in five months that the lung had begun to re-expand. Repeated aspirations were done and on April 26, 1950 it was noted that the lung had expanded almost to the chest wall (Figure 2). On May 8, 1950, 10 cc. of fluid were removed and on culture no pyogenic organisms were found. One hundred thousand units of streptokinase and 40,000 units of streptodornase were again introduced into the pleural cavity. On the following day, 100 cc. of yellowish pus were removed. Again he had a febrile rise up to 102 degrees F. for three days. On May 20, 1950, 100 cc. of thick purulent exudate were removed. An x-ray film on May 24, 1950 (Figure 3) showed an increased amount of fluid over the previous film, but his lung again was expanding. On May 27, 1950, 140 cc. of thin turbid fluid were removed. On June 18, 1950, 25 cc. of fluid were removed, which on culture still showed tubercle bacilli. Aspirations were continued up to August 9, 1950 with gradually decreasing amounts of fluid being

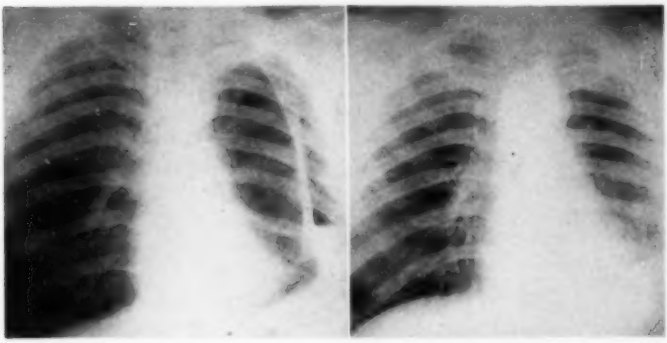

FIGURE 1 FIGURE 2

Figure 1: Tuberculous empyema, March 22, 1950. Note thickened pleural membrane.—*Figure 2:* April 26, 1950. Pleural membrane thinned. Lung expanding following use of enzymes.

obtained. After August 9, 1950 all attempts to aspirate resulted in dry taps. At that time the lung had expanded to the chest wall and Figure 4 (November 30, 1950) shows the present status of the patient. The fixation of the left diaphragm was present for several weeks prior to the instillation of the enzymes solution.

Since August of 1950 the patient has been clinically well, has been afebrile and has gained 50 pounds. During the course of the treatment of empyema, he was on an out-patient basis, coming to the hospital or office for aspirations. He has been working for the past few months.

Discussion

The tuberculous empyema was a complication of the artificial pneumothorax. Fluid was present early in the course of the pneumothorax, and two years after the start of therapy, tubercle bacilli were demonstrated in the fluid. Sixteen months later the fluid became purulent, the lung became non-expandable, and pneumothorax had to be discontinued. At this time, it had been planned to discontinue the pneumothorax anyway since the lung lesion was apparently healed, but in spite of repeated aspirations, the lung remained fixed. Since the parenchyma of the lung was clear, it was felt that its failure to expand was due to a fibrinopurulent exudate which encased the lung. On rare occasions, repeated aspirations of tuberculous empyema with or without the use of antiseptic solutions has resulted in a cure. However, it is inconceivable that, in the presence of a non-expandable lung, this could occur. Aspirations were done for five months and failed to effect expansion of the lung. The next step would have been thorocoplasty. Following the instillation of streptokinase-streptodornase, however, there was immediate expansion of the lung, and within four months the empyema had disappeared and has not

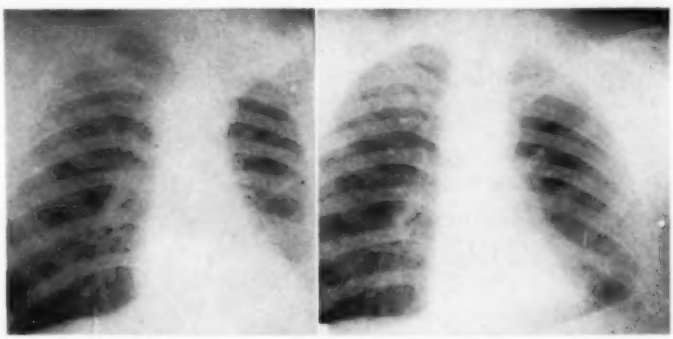

FIGURE 3 FIGURE 4

Figure 3: May 24, 1950. Increased effusion following second instillation of enzymes.—*Figure 4:* November 30, 1950. Complete expansion of lung except for diaphragmatic adhesion persistent throughout.

recurred after nine months. It can be concluded, therefore, that streptococcal concentrates may in selected cases be effective in the treatment of tuberculous empyema.

When irreversible pathological changes take place in the lungs and pleura, or when bronchial fistulae are present, the enzymes can not be expected to be curative, since restoration of pulmonary function under these conditions is not possible. Even in such cases, however, Tillett[2] has shown striking results in clearing of infection in conjunction with surgical procedures. Streptokinase-streptodornase should be used early in the course of tuberculous empyema before irreversible changes have taken place. It is conceded that this form of therapy may be applicable in only a minority of the cases of tuberculous empyema and may be most effective in the type complicating artificial pneumothorax.

SUMMARY

A patient with tuberculous empyema and non-expandable lung was treated by the pleural instillation of streptococcal concentrates containing streptokinase-streptodornase. The enzyme therapy resulted in prompt expansion of the lung and disappearance of the empyema following aspirations. The enzyme solution may be specific in the treatment of tuberculous empyema when used before irreversible pathological changes have taken place.

RESUMEN

Un paciente con un empiema tuberculoso y un pulmón que no expandía fué tratado por medio de la instilación pleural de concentrados estreptocócicos que contenían estreptokinasa-estreptodornasa. La terapia enzímica dió por resultado la pronta expansión del pulmón y la desaparición del empiema, después de aspirar. La solución de la enzima puede ser específica en el tratamiento del empiema tuberculoso, si se emplea antes de que sobrevengan cambios patológicos irreversibles.

RESUME

Un malade atteint de pleurésie purulente tuberculeuse et dont le poumon avait perdu toute possibilité d'expansion a été traité par des instillations intra-pleurales d'un extrait de streptocoques, contenant de la streptokinase-streptodornase. Ce traitement fut suivi d'une rapide expansion du poumon, et de la disparition de l'empyème après aspiration. Il semble que la solution enzymatique soit un traitement spécifique de la pleurésie purulente tuberculeuse, quand elle est utilisée avant que des altérations anatomiques irréversibles se soient constituées.

REFERENCES

1 Tillett, W. S., Sherry, S., Christensen, L. R., Johnson, A. J. and Hazelhurst, J.: "Streptococcal Enzymatic Debridement," *Ann. Surg.*, 131:12, 1950.

2 Tillett, W. S.: Personal communication.

Announcement

Recently a great deal of public interest has been directed to a new compound for the treatment of tuberculosis. This substance, which is isonicotinic acid hydrazine, and is manufactured under two names, Rimifon (Hoffmann-La Roche Inc.) and Nydrazid (E. R. Squibb & Sons), is the latest of a series of drugs for the treatment of tuberculosis.

There have been extensive experiments performed on animals which indicate that this drug is active against the tubercle bacillus. The carefully conducted and controlled investigative work done at the Sea View Hospital, New York, Cornell University and Saranac Lake indicates that tuberculosis in the human being responds to this medication.

There has not been enough work or enough cases treated to be able to determine how this drug will fit into the present day treatment of tuberculosis. If all the early promise is fulfilled, we still cannot say whether this drug will represent a treatment of itself or whether it will remain as another adjunct to the various methods now used by chest specialists in the treatment of tuberculosis. Other questions yet to be answered are whether this drug will extend the scope of treatment, decrease the time required, or change the approach to certain types of this disease. It is strongly recommended that until some of these questions have been answered, Rimifon and Nydrazid be used only in an experimental manner in cases properly selected and controlled.

In this issue of *Diseases of the Chest* is reported the work on Rimifon and Marsilid, which is a nicotinic acid hydrazide derivative, by a group of research workers at Hoffmann-La Roche Laboratories and Sea View Hospital. In the current issue of the *American Review of Tuberculosis* another series of articles on these drugs has been published, in addition to clinical and laboratory reports of work performed at Cornell University with Nydrazid, the E. R. Squibb Company product.

At a conference held in New York City on January 8, attended by representatives of the *American Review of Tuberculosis, Sea View Quarterly Bulletin* and *Diseases of the Chest,* it was agreed that these articles would be published simultaneously in the three journals and would represent the first public announcement of these drugs. Both manufacturers and all the investigators have expressed their regrets that the drug was publicized through non-medical channels prior to this publication.

A great deal more work has already been started and it is expected that the results of this and additional clinical and laboratory investigations will appear in the pages of *Diseases of the Chest* and other medical journals in the near future.

Council on Management and Treatment of Diseases of the Chest.

Eighteenth Annual Meeting of the College

The 18th Annual Meeting of the College will be held at the Congress Hotel, Chicago, Illinois, June 5 through 8, 1952. Members who plan to attend the meeting and who have not as yet made arrangements for hotel accommodations are urged to write to the Congress Hotel immediately for reservations.

The annual motion picture session on diseases of the chest will be presented on Friday evening, June 6. Dr. Paul H. Holinger is in charge of this session and members are invited to submit films for consideration. Please send films to Dr. Paul H. Holinger, 700 North Michigan Avenue, Chicago 11, Illinois.

The annual x-ray conference will be held on Saturday, June 7, Dr. Leo G. Rigler will serve as moderator. Physicians who plan to attend the meeting are invited to submit interesting cases for the conference. The cases must be proven by biopsy, surgery or autopsy, and may cover any subject of interest in chest diseases. Please send a concise summary including the pertinent history, physical findings and laboratory work, and the final pathological proof, together with your x-ray films to Dr. Leo G. Rigler, Department of Radiology, University of Minnesota Medical School, Minneapolis 14, Minnesota.

College Chapter News

NEW YORK STATE CHAPTER

The annual clinical meeting of the New York State Chapter of the American College of Chest Physicians was held at the Hotel New Yorker, New York City, Thursday, February 21, 1952. One hundred sixty-five physicians from New York, Pennsylvania, New England states and Canada attended.

The Executive Committee of the New York State Chapter voted to present College Keys to each of the past presidents of the chapter.

The annual meeting of the New York State Chapter will be held on May 15, in New York City. Dr. Andrew L. Banyai, President Elect of the American College of Chest Physicians, has been chosen to deliver the Howard Lilienthal lecture.

The Executive Committee announced that the next annual clinical meeting of the Chapter will be held at the Hotel New Yorker in New York City on February 19, 1953. The scientific arrangements committee for this meeting is composed of Dr. Hyman Alexander, Chairman, Dr. James S. Edlin and Dr. Irving Shiner.

Harry Golembe, M.D., Secretary-Treasurer.

VIRGINIA CHAPTER

Dr. W. E. Roye, Program Chairman of the Virginia Chapter of the American College of Chest Physicians, announces that a scientific program will be held at the Hotel Roanoke, Roanoke, Virginia, during the afternoon of Wednesday, May 7, 1952.

Following the scientific program, there will be a social hour and dinner for members, wives and guests.

Fifth Annual Meeting, Argentine Chapter, American College of Chest Physicians, Punta, Lara, Argentina, December 1, 1951.

ARGENTINE CHAPTER

On December 1, the Argentine Chapter of the American College of Chest Physicians held its Fifth Annual Meeting in the city of Punta Lara. The there of the scientific program was:

TUMORS OF THE MEDIASTINUM

"Pathological Grouping and Histogenetic Classification,"
Angel N. Bracco and Moises Polak.

"Symptomotology and Diagnosis,"
Mahelz Molins and Guido Pollitzer.

"Surgical Treatment of Tumors and Histopathological Study of the Extirpated Specimens,"
Lazaro Langer and Alberto J. Herrero.

Other papers were presented by Oscar Jose Cames and Alfredo F. J. Cesanelli; Oscar A. Vaccarezza; Andres A. Santas, Mario Samuel Brea and Rotjer; Mario Samuel Brea and Jorge A. Doyley; J. Mainetti and Jorge Alberto Taiana.

Following the scientific session, Dr. Francisco Arambarri presented the annual secretary-treasurer's report and Dr. Paulino A. Rojas gave his address as the retiring president of the chapter.

The following officials were elected for 1952-1953:

Dr. Tomas de Villafañe Lastra, Córdoba, President
Dr. Rodolfo E. Cucchiani Acevedo, Buenos Aires, Vice-President
Dr. Isaac Wolaj, Córdoba, Secretary-Treasurer.

It was voted to hold the Sixth Annual Meeting of the chapter in Córdoba in 1952.

ISRAELI CHAPTER

The annual meeting of the Israeli Chapter of the American College of Chest Physicians, held jointly with the Israeli Phtisiologists, took place at Raanana Hospital on September 12, 1951. Those participating were Dr. Leo G. Rigler, Minneapolis, Minnesota; Prof. Carl Semb, Oslo, Norway; and Prof. Erik Warburg, Copenhagen, Denmark.

The following papers were presented:

"The Development of Thoracoplasty,"
Carl Semb, Oslo, Norway.

"The Problems of Tuberculosis in Denmark,"
Eric Warburg, Copenhagen, Denmark.

"A Concept of Phtisiogenesis,"
Hugo Adler, Raanana.

"Cystic Disease of the Lung,"
Herman Lichtenstein, Haifa.

"Segmental Resection in Pulmonary Tuberculosis,"
Yehuda Pauzner, Tel-Aviv.

"Conservative Treatment of Tuberculous Empyema,"
Maurizio Mendes, Jerusalem.

At the conclusion of the meeting a luncheon was given at Raanana Hospital, attended by the guests from abroad and representatives of all the medical institutions in the country.

The following officers were elected for the coming year: Hugo Adler, Raanana, President; Joseph Weiser, Neveh-On, Vice-President; Wilhelm J. Hupert, Ramatajim, Treasurer; and Abraham Zifroni, Safed, Secretary.

CALIFORNIA CHAPTER

The annual meeting of the California Chapter of the American College of Chest Physicians will be held at the Beverly Wilshire Hotel in Beverly Hills, California, on Saturday, April 26, 1952. Dr. Alfred Goldman, Program Chairman, has announced the following scientific session:

MORNING SESSION — 9:00 a. m.

Moderator — Carl Howson

"Differential Diagnosis of Congenital Heart Disease,"
Morse J. Shapiro, Beverly Hills.
Discussant: Lewis Bullock, Los Angeles.

"Selection of Patients with Pulmonic Stenosis for Surgery,"
David Levinson, Alfred Goldman, Morley J. Kert, Maurice Rosenfeld, Jack A. Sheinkopf and Jerome N. Sugarman, Los Angeles.

"Evaluation of Results of Surgery for Mitral Stenosis,"
Jack A. Sheinkopf, Alfred Goldman, Morley J. Kert, David Levinson, Maurice Rosenfeld and Jerome N. Sugarman, Los Angeles.

"Clinical Findings and Pathology in 1070 Autopsies of Patients with Bronchiogenic Carcinoma,"
Seymour M. Farber, et al., San Francisco.
Discussants: Lewis W. Guiss, Los Angeles,
Irving Reingold, Long Beach.

"Experimental Tracheal Implants,"
W. P. Longmire, Jr., Wm. H. Muller and
Joel J. Pressman, Los Angeles.

"The Nature of the Wolff Parkinson White Syndrome,"
(Illustrated by Colored Motion Pictures).
Rexford Kennamer, Eliot Corday, Joshua Fields, John A. Osborne, Myron Prinzmetal and L. Allen Smith, Los Angeles.

LUNCHEON — 12:00 Noon

Luncheon Speaker: George C. Griffith, Professor of Medicine and Coordinator of Cardiovascular Department of the University of Southern California Medical School, Los Angeles.

Subject: "Recent Advances in the Field of Cardiovascular Diseases."

AFTERNOON SESSION — 2:30 p. m.

Moderator — Edward W. Hayes

"Pulmonary Tuberculosis—Gastric Lavage, Tracheal Wash and Laryngeal Swabs in Diagnosis,"
Harold G. Trimble, Oakland, and Buford Wardrip, San Jose.
Discussants: Donald Ash, Oakland; Emil Bogen, Olive View.

"Differential Diagnosis of Surgical Disease of the Esophagus,"
Benson B. Roe, San Francisco.
Discussant: Orville Grimes, San Francisco.

"Segmental Resections in Pulmonary Tuberculosis,"
Lyman A. Brewer III, and Frank S. Dolley, Los Angeles.

"Evaluation of 95 Consecutive Pulmonary Resections for Tuberculosis,"
E. J. Shabart and Paul C. Samson, Oakland.
Discussants: W. L. Rogers, San Francisco,
John C. Jones, Los Angeles.

"Bronchography with the Aid of Water-Soluble Radiopaque Xumbrodil,"
Jacob Abowitz, Duarte.
Discussants: Lt. B. Barton, M.C., Oakland,
Marvin S. Harris, Los Angeles.

"Transthoracic Approach to Upper Abdominal Lesions,"
Elmer Rigby, Los Angeles.

COLORADO CHAPTER

The Colorado Chapter of the College held a clinical x-ray symposium at the Shirley-Savoy Hotel, Denver on December 8, 1951.

On April 5, 1952, an x-ray clinical symposium will be held at the Fitzsimons General Hospital at 1:30 p. m. Colonel C. W. Tempel will moderate this program.

Plans are being made for the annual meeting of the Chapter to be held in Estes Park on September 13, 1952. This meeting will be held in conjunction with the Annual Meeting of the Colorado State Medical Society.

Committee on College Resident Fellowships

The Committee on College Resident Fellowships has announced that there has been established three active fellowships: the S. H. Camp and Company Fellowship, Jackson, Michigan; the United Fruit Company Fellowship, New York City; the Dr. Alfred S. Richman Fellowship, New York City. These fellowships provide funds to allow travel and a small stipend for physicians from other countries whose applications have been approved by the committee.

College News Notes

The College News Section of *Diseases of the Chest* is devoted to the activities of the members. Kindly send all news items to the American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.

Dr. Amadeo Vicente Mastellari of Panama City, Regent of the College for Central America, has been appointed one of the seven members of the Executive Advisory Committee of Tuberculosis for the World Health Organization.

Doctor John Briggs of St. Paul, Minnesota, was elected vice-president of the Minnesota Society of Internal Medicine.

Doctor Walter E. Vest of Huntington, West Virginia, was reelected chairman of the Medical Licensing Board for a two year term. He was the first chairman of the Board which was organized in 1949.

Doctor Leo J. Rigler of Minneapolis, Minnesota, recently returned from a two month tour of Israel and Iran. He made the trip as a member of a fourteen-man medical mission sent out by the World Health Organization and the Unitarian service committee to explain the latest advances in treating patients and teaching medical students.

Doctor Hyman Sapoznik of Chicago, Illinois, recently returned from a two week tour of Israel. He attended a meeting of the Israeli Chapter and presented a paper on "Antibiotics in Pulmonary Tuberculosis."

Faculty and College officials participating in the Second Postgraduate Course on Diseases of the Chest held in Havana, Cuba, December 17-22, 1951.

SECOND POSTGRADUATE COURSE ON DISEASES OF THE CHEST, HAVANA, CUBA

The second postgraduate course on Diseases of the Chest was held in Havana, Cuba, December 17-22, 1951, at the amphitheater of University Hospital, Calixto Garcia, under the sponsorship of the Council on Postgraduate Medical Education and the Cuban Chapter of the American College of Chest Physicians, with the assistance of the Cuban Minister of Health, the representatives of the scientific societies and the University of Havana.

An outstanding attraction of this successful postgraduate course was the use of television. The televised portion of this course emanated from the operating room of the Hospital Sanatorio La Esperanza. The use of television was made possible through the courtesy of "Union Radio," under the direction of Mr. Manolo Alonso. This is the first time the television has been used in a postgraduate course sponsored by the American College of Chest Physicians.

Dr. Norman J. Wilson of Brookline, Massachusetts, presented a paper entitled, "Results of Pulmonary Surgery." This presentation was followed by a question and answer period. A board of experts, consisting of the instructors, also answered questions presented by the physicians who attended this course.

The luncheon for the instructors and students was held at The Salones del Casino Español of Havana. At the luncheon, certificates of merit were presented to the founders of the Cuban Chapter. Plans are now being studied for the Third Postgraduate Course to be held in Havana, Cuba, during the latter part of 1952.

Obituaries

HENRY WATSON

1880 - 1951

Dr. Henry Watson, who died at Parkes, New South Wales, Australia, January 5, 1951, at the age of 70, had spent the major portion of his life in Australia practicing in tuberculosis.

Dr. Watson graduated in Medicine at the University of Aberdeen in 1902, and after serving on the staffs of various Scottish hospitals, occupied the position of a civilian surgeon at one of the Army hospitals in Scotland during the First World War, 1914-1918. He emigrated to Australia shortly after the conclusion of hostilities, and after engaging in general practice for a short time, he was, in 1928, appointed as the first Medical Superintendent of Heatherton Sanatorium, Victoria, Australia. He continued as Medical Superintendent of this Sanatorium until his retirement in 1946, when he engaged in private specialized practice in tuberculosis. Following a coronary occlusion in 1949, he gave up practice and lived in the country until his death early in 1951.

Despite his long sojourn in Australia, Dr. Watson remained a dour Scot throughout his life. He had little academic specialized training, but his years of experience in handling Heatherton Sanatorium provided him with a wealth of clinical knowledge and understanding of the

psychological difficulties which play such a large part in affecting the course of the disease in female patients. His death has lost to Australia tuberculosis work, a colorful personality and a generous friend, but he has left his mark in sanatorium control in the state of Victoria.

The sympathy of his colleagues is extended to his daughter, who must be gratified by the respect and affection her father had engendered in the patients to whom he devoted his life and interest.

Alan H. Penington, Governor for Victoria, Australia.

JOHN NANTS WILSON

1900 - 1951

After twelve days' illness at Mt. Alto Hospital, Washington, D. C., Dr. John N. Wilson died November 3, 1951. Dr. Wilson had been Assistant Chief of the Tuberculosis Division at the Washington Central Office of the Veterans Administration since June 1948.

He was born in Landover, Maryland, and had been living at 1224 North Adams Street, Arlington, Virginia, since his return to Washington, where he had taken his medical degree and his internship at George Washington University in 1927 and 1928. He also served as a resident at St. Elizabeth's Hospital in Washington. He had previously served as a Corporal of the U. S. Marine Corps in France, in World War I, and the Corps was represented at the burial in Arlington Cemetery.

He entered the Veterans Administration Tuberculosis Service at Rutland Heights, Massachusetts in July 1929, serving there until his promotion to Clinical Director at Castle Point, New York in July 1937. He next served in the same position of responsibility at Outwood, Kentucky, until his call to Central Office as Medical Adviser to the Insurance Claims Service in April 1940. It was from this position that he was called to the Managership of the Rutland Heights Hospital in January 1945, and it was under his humane leadership that this hospital contributed to a number of our present advances in the field of tuberculosis. While there, he helped develop a program of patient education in cooperation with and financed by the State and other local tuberculosis associations. His "Methods Used to Improve Hospital Facilities" was presented at the National Tuberculosis Association's 50th Annual Meeting in New York, 1948, and is printed in the Transactions of that year.

He served on the Committee on Diagnostic Standards of the American Trudeau Society during the time the 1950 edition was developed and published. He was a Fellow of the American College of Chest Physicians and of the American Medical Association.

Arden Freer, Governor for the Veterans Administration.

COLLEGE EVENTS

18th Annual Meeting, American College of Chest Physicians, Congress Hotel, Chicago, Illinois, June 5-8, 1952.

Illinois Chapter Meeting, Chicago, April 4, 1952.

California Chapter Meeting, Beverly Hills, April 26, 1952.

Texas Chapter Meeting, Dallas, May 5, 1952.

New Jersey Chapter Meeting, Atlantic City, May 20, 1952.

XII Congress, International Union Against Tuberculosis
II International Congress on Diseases of the Chest
Rio de Janeiro, Brazil, August 24-30, 1952.

Chicago Postgraduate Course, October 6-10, 1952.

New York Postgraduate Course, November 10-15, 1952.

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POSITIONS AVAILABLE

Two residents wanted for 175 bed Ohio tuberculosis hospital approved for residency. Salary $250.00 per month less nominal charge for maintenance. Single physician preferred. One vacancy April 1, 1952. One vacancy June 10, 1952. Please address Box 242A, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.

Assistant medical director for 600 bed hospital in South Central state. Salary $7,500 per year, plus complete maintenance. Graduate of American Medical School desired; well rounded training in tuberculosis required. Please address Box 243A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Staff physician wanted for Ohio county tuberculosis hospital. Experience in tuberculosis and Ohio State License necessary. Salary $7,000 to $8,000, plus furnished house. Apply to Box 244A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Resident wanted for 100 bed tuberculosis hospital. Salary $275 per month. Please address Box 245A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Internist trained in diseases of the chest needed in one of the New England States. Private practice in addition to small sanitorium. For further information please address Box 246A, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.

POSITIONS WANTED

Thoracic and general surgeon, age 34, has seven years' training, two in thoracic surgery including tuberculosis. Passed Part I Surgery. Available in July. Desires association, partnership, institutional appointment with opportunity for private practice. Please address Box 261B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Thoracic surgeon, age 36, certified American Board of Surgery, eligible Board of Thoracic Surgery, desires full or part time position in sanatorium or group. Vast experience in modern tuberculosis and general thoracic surgery. Outstanding references. Please address Box 262B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Chest specialist, age 35, F.C.C.P., eligible board on internal medicine, desires responsible position in or near large city with group, associate, or sanatorium. Available July 1952. Excellent references. Please address Box 263B, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Illinois.

ANNOUNCEMENTS

Nutley, N. J.—Roniacol Elixir 'Roche' is a new, potent, well-tolerated liquid vasodilator. This palatable elixir provides 50 mg. of Roniacol per teaspoonful in a port wine flavored vehicle. Clinical studies have demonstrated the usefulness of Roniacol in various vasospastic disorders, including some cases of angina pectoris. Richter et al. recently observed (*New York State Journal of Medicine*, 51:1303, 1951) that "Roniacol appears to be more effective as a vasodilator in arteriosclerosis obliterans than other known drugs in common use." Chemically, Roniacol is beta-pyridyl-carbinol (the alcohol corresponding to nicotinic acid).

Synkayvite-CB Lozenges 'Roche' are new, cherry-flavored, candy-like lozenges which provide Synkayvite (vitamin-K compound) for prevention of delayed hemorrhage, vitamin C for promotion of wound healing and B-complex factors for reinforcing the nutritional status of the patient. Synkayvite-CB Lozenges are especially valuable in young patients following tonsillectomy when swallowing may be difficult. Recent clinical studies, such as that of King (*Southern Medicine and Surgery*, 113 : 186, 1951) have stressed the value of vitamins K, C and B-complex in preoperative and postoperative care. Synkayvite - CB Lozenges provide these factors in highly convenient and pleasant dosage form. Chemically, Synkayvite (water-soluble vitamin K compound) is the tetrasodium salt of the diphosphoric acid ester of 2-methyl-1, 4-naphthohydroquinone.

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